بسم الله الرحمن الرحيم

Granulomas

(Basics)

- **Def.:** Compact or organized collection of **Histiocytes** ± may be associated ± Accessory features as ← Caseation / Infilt. by other cells.

- Histiocytes are Tissue Macrophages that derived From Blood. **Monocytes** → Tissue → Histocytes (2 Types)

  - Macrophage
    - (F) phagocytosis
  - APCs
    - (F) Ag presentation (ex Langer. Hans cells)

In granuloma Histiocytes take 3 Types

1. **Histiocytes**
   - Rounded or oval
   - Cytoplasm: Abundant Eosinophilic
   - Nucleus: large, pale, oval, vesicular
2. **Epithelioid Cells**
   - (Epithelial or KC like = Tall cells)
   - Represent Activated Histiocytes ± Morphological changes.
3. **Multinucleated Giant Cells**
   - Aged macroph: due to fusion of Many Histiocytes or Epithelioid Cells.

- They Have Surface Rs ← For phagocytosis, Complement, Fc of IgG.

"ماهي تواريخها"

- Granuloma develops as an Immunological response to non-degradable (undigestable) Ag ± Drugs, Infect., FB, etc..

Classification

(1) FB or Allergic
(2) Infectious or Non Infectious
(3) Pathological
   (i) Nodular
   (ii) Diffuse

Pathological Classification.

• Nodular

✓ A. Tuberculoid (epithelioid Hist. + Lymphocytes).

- TB
- Lepr
- Ø
- Leishmania
- Rosacea (granulom.). (perifollicular)
- LMDF. (Peri-follicular).

✓ B. Sarcoidal (Naked)

- Sarcoidosis
- Sarcoidal FB — Silica / Zirconium
- L-Nitidus.

✓ C. Palisading : ✓

• Diffuse

(A) Suppurative

1. Deep fungal Inf.
2. Atypical Mycobact.
3. Actinomycosis
4. Halogenoderma

(B) Foamy.

1. Xanthoma
2. XG
3. Leprosy (HL)
4. Reticulohistiocytoma.

Multinucleated Giant Cells

- formed by fusion of Multiple < Epithelioid Cells (Epithelioid Macrophages) — Macrophages (Histiocytes)
- Types:
  - Langhan Giant Cells: Nuclei arranged orderly at periphery (Horse shoe) → 
  - FB Giant Cells: Nuclei arranged Randomly in the Cytoplasm 
- Function: Trapping disposable unnecessary mononuclear Cells Entering area of Inflamm.

Multinucleated Giant Cells

(Epithelial)

1. Epidermal Giant Cells : HSV
2. Langhans multinuc. Giant Cells
3. F.B Giant Cells
4. Touton Giant (Xanthomas (sp. JXG))
5. Melanocytic Giant Cell. (Eg. Mc. NEVI & melanoma)
6. Endothelial Giant Cells (CMV)
7. Reed-Sternberg cells (*See Lymphoma)

Classification of Granuloma

A Etiological Classification

- Granuloma
  - Foreign-body granuloma
    - Exogenous: Oil, starch, silicon, ... etc.
    - Endogenous: Keratin, sebum, urates
    - Foreign-body G. shows: (3)
      - Histiocytes
      - Few or no epithelioid cells
      - Giant cells (large with irregular arrangement of the nuclei) → FB Giant Cells.
  - Allergic granuloma
    - Infectious: TB, leprosy, syphilis, deep fungi
    - Non-Infectious: Sarcoidosis, Palisading Gran.
    - Allergic G. shows: (2)
      - Epithelioid cells
      - Multinucleated giant cells (Langhans) with small horse-shoe nuclei

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- Funct of Granuloma: it is considered as Type IV Hypersensitivity reaction to Isolate or Eliminate An. Ag.

· Classification of Mycobacteria.

- **Slow growers** (2-3 wks)
  - (i) **photochromogens**: مستعمرات صفراء عند التعرض للضوء
    - M. Marinum
    - M. Kansasii
  - (ii) **scotochromogens**: مستعمرات صفراء بدون التعرض للضوء
    - M. Scrofulaceum → لا-ن
  - (iii) **Non-chromogens**:
    - M. TB & Bovis, BCG
    - MAIC, ulcerans, Hemophilum
- **Rapid growers** (3-5 days / 7 days)
  - M. Chelonae, Abscessus, fortuitum
- **Non-Cultured**
  - M. Leprae

Mycobacterial Infection

(Myco = produce mold like Thin growths on liquid media)

- Group of bacteria ch By.
  - Aerobic, Intracellular
  - Slender (Curved Rods)
  - Non motile
  - Non Spore forming
  - Resist staining (d.t lipid rich cell Wall) & Lysosomes.
  - Resist decolorization by acid & alcohol (after staining) → So called Acid fast & Alcohol fast.

- Structure: have cell wall the Contain: Large amount of lipids as:
  - Mycolic acids.
  - Fatty acids.
  - other lipids

↓

1. Ability to retain "Carbol Fuchsin dye" after washing by acids & Alcohol → So Called

Or

Resist decolorization ⇐ Acid fast & Alcohol Fast

by < acid / Alcohol

2. Resist Lysosomal Attack.

NB

Other Alcohol & acid fast:
- Nocardia
- Cryptosporidium.

- Types:

A
- Typical → TB & Leprosy
- Atypical → inf. other than TB or Leprosy

B According to the Culture
- (1) Slow growers (2-3 w.)
- (2) Rapid " (3-5 d.)
- (3) Non-Cultured.

NB

- TB: Stain
  - (i) Z.N: specific, Not Sensitive (Need 10.000 organism/ml)
  - (ii) Auramine Rhodamine More Sensitive

TB of the Skin

- Rare dis. caused by Mycobact. TB (Atypical)
- Represent [1% of Extrapulm. TB.
  [4% of all Cases of TB
- Predisposing factors (↓↓ CMI):
  - Cytotoxics.
  - Cs.
  - Lymphoma.
  - Malnutrition.
  - HIV.
- Risk is 500 Times Higher than in NL People
- Mainly d.t. M. Avium & M. Kansasii
- Less Common: M. TB
- Onset < M. Avium: occurs Late when there is marked ↓ CD4.
  < M. TB: occurs Early.

• 1ry TB Complex:

Primary Sites of TB±:

1. Lung (Inhalation)
2. Tonsils (Ingestion)
3. Skin (if Inoculation or Haem. or Lymph. Spread) = (From Skin → Skin)
4. Intestine. (M. Bovis)

- M. TB Complex (3 strains are pathogenic to Human)
  1. M. TB (95% of TB inf. in Human)
  2. M. Bovis (Transmitted From Cattle to Human via milk)
  3. BCG

Cutaneous TB

- There are 2 forms of TB Inf. of the Skin:
  (Tuberculoderma):
  - (A) True Tuberculoderma: Actual Invasion by Bacilli
  - (B) Tuberculid: Allergic Reaction to Bacilli or their products.

True Tuberculoderma:

- Can be classified acc. to:
  1. Mode of Inoculation
  2. Host Immunity.

① Exogenous:
- TB chancre. (TBC)
- TVC.

② Endogenous:
- (i) Autoinoculation: TCo
- (ii) Contiguous spread: SF
- (iii) Hematogenous / Lymphatic:
  - LV
  - Acute miliary TB.
  - TB Gumma.

- Most Common (type):
  - TVC
  - LV
  - SF

The Most Common Types in: (i) Children: SF
(ii) Adults:

- Chr. Hg. malnourish
- Single or multiple
- Nodule → ulcerate & Fistula

Acc. to host immunity:

- Good Immunity
  1. LV
  2. TVC
  3. Tuberculida.
  - ++CMI
  - T Lymphocyte
  - ↓ Caseation & Bacilli
- ③ (Paucibacillary TB)
- Poor immunity ④ (Multibacillary TB)
  - SF
  - TCo
  - TB Gumma
  - Acute miliary

اسهل كلش باختصار عن كل نوع

TB. Chancre (1ry Cut. Complex $\xrightarrow[To]{Correspond}$ Gohn's focus)

Inoculation of FaCe LL mm → 2-4 w. → Cut. lesion → 3-8 w. → L.N

- Rare cut TB of skin d.t direct exogenous inoculation of organism into the skin or mm of an individual who has (Neither): Natural Nor artificially Acq. Immunity (BCG)

Direct inoculation

↓ 2-4 w.

Skin lesion + L.N

asympt, red-brown papule or nodule → ulceration (Painless, Bluish Margin, Necrotic & G.T of Floor, Indurated Base)

Painless & Indurated ← (Cr) 2 w.

↓

Fate

If good immunity:

↓ Early Healing (1-3 ms)

T cells destroy the bacilli & granuloma formation 3-12 ms

Healing by scar. + Calcified regional L.N

- Tuberculin: . Early: −Ve
  . Later: +Ve

If bad immunity:

↓

- The organism remains Latent & Later reactivate &
- May Evolve into:
  - L.V
  - L.TVC
  - e.S.F.
  - Miliary TB.

TB Verrucosa Cutis = Warty TB. (Anatomists / Butchers Wart) (Verruca necrogenica)

- Def: TB inf. of skin (d.t) Exogenous inoculation of the organism in patients who had Acq. Imm. (either d.t previous inf. or Immunization) — either: Natural / Artificial
- Site: Hands (but any site ± affected)
- CIPs: · Hyperkeratotic, Warty, Verrucous Plaque
  · ± Peripheral extension & Central Fissuring, Crusting & Scarring .. No L.N .. (±) Spont. Healing & Scar
- HP: (i) Hyperkeratosis
  (ii) PEH
  (ii) Dermal:
  - Abscession
  - Granuloma: Giant Cells, No Bacilli

TB Scrofuloderma (SF) (Most Common Type in Children)

- TB infection of the skin d.t "contagious endogenous" Extension from an underlying infected Tuberculous:
  - LN (commenst, usually Cervical & axillary) ← M. Bovis → Tonsillar & oral lesion → Cervical aden. → Cold Abscess → Sepsis to skin.
  - Bone
  - Joint or
  - Epididymis. (post-scrotal ulcer)
- CIP: . the Most Common sites are: lat. Neck & Parotid area. Bluish SC Nodule → Accumulate Pus & Exudate (Cold Abscess) → ulceral (ثقوب) & Sinus formal — Healing → puckered or hypertrophic scar.
- DD of Axillary lesions: H. Suppurativa

TB Gumma (Metastatic TB abscess): Variant of scrofuloderma

that occurs d.t Hematogenous spread of Mycobacteria to skin

CIP: Single or Multiple Painless s.c (Abscesses) — break down → Fistulas & ulcers (as in SF). Rarely: Malnourished children at Extremities.

6

حوالنقات (3) الجسم

• Tuberculosis Cutis orificialis (TCO) → ulcer

- TB Inf. of skin & MM adjoining the body orifices.

- ↓ Autoinoculation:
  - Pulmonary TB → autoinoculate → orofacial TB
  - Intestinal TB → perianal TB
  - Genitourinary TB → penile & vulvar

- Orbital TB: (commonest): Tongues usually affected (R Tb & Silver) & may be Tooth Socket after Extraction

Oral Ulcer: very painful very resist

- lesion: Red Papule → (Multiple) painful soft punched out shallow very painful ulcers (orifices) (Not tendency for spont. Healing).
- NB: Pts. usually: Elderly. have severe Inf. organ disease & appearance of TCO → Poor prognosis.

احظ لوبس → • Lupus Vulgaris (LV) → Local

- The 2nd Most Common Type of Cut. TB, starting in Childhood & progress. & occurs in pts ē Very good imm. "Tuberculin Test (++Ve)"

Epidemiology: Age 20–40; Sex: M > F (3 : 1); (CS Sarcoid)

- It occur as a result of:
  1. Exogenous: re-infection of previous TB chance (the organism may remain latent & then reactivated → LV)
  2. Endogenous (+++)
  3. Obscure Route??

Haematogenous / Lymphatic: from mucosa → Nose / Throat
direct: from underlying Joint / Gland

C/P

- Origin: Either on Top of NL skin (more common) or on Top of ↖ BCG, SF, TVC

- Site: Commonly: Neck & face ss. ↖ Nose, cheeks, Ear lobes
  Less common: buttocks & limbs. (in Tropics common.)

What is LV Lesion?

Single plaque composed of Papules & Nodules:

-- Soft (Apple-jelly like).

- Reddish - brown in color
- Diascopy test → « apple jelly color » [yellow brown spots]

The plaque:
- Periphery: → Serpigenous Extension
- Center: Scarring, thin, contractile, unhealthy

(new lesion strip appears on areas of atrophy).

• clinical Varieties:

1. Plaque forms: Psoriasiform ē No ulcerate Nor Scarring.
2. Nodular (Tumiform): large soft Tms on ear lobes with No ulcerate Nor Scarring
3. Vegetative: Necrosis, ulcerate [with] minimal Scarring
4. ulcerative & Mutilating: marked ulcerate, Scarring & Crust form ate → Deep tissue & Cartilage invasion → Contracture & deformities.
5. Mucosal.

- Complications of LV: (Lupus Vorax)

1. Scarring & destruction of ← Cartilage e.g. Ear & Nose
   ← MM: Nose, oral } microstomia; Eye → Ectropion.
2. Reactivation after apparent healing (unhealthy scar).
3. Mg Transformation: SCC (++) & BCC (+)

destruct^ / Reactivat^ / Mg Transformat^

(Pathology) → Tuberculoid Granuloma: (upper dermal)

- Epithelioid cells
- Langhans Giant cells
- dense mononuclear (Lymphocytes & monocytes)
- infilt. ē Slight (or) Absent

(±) Caseation (minimal) — TB bacilli (-ve) (Absent).

- Epid. Changes as: Atrophy, Hypertrophy & Hyperplasia, ulcer.

- DD of Tuberculoid Granuloma

- TB
- TT
- Sarcoidosis

| Deep Sarcoid

- FB Granuloma
- Deep Fungal Inf.

- LMDF
- Granulomatous Rosacea
- Atypical Mycobact
- Ø

PLEVA like

Acute - Miliary TB ← Immuno compromised & Hemafagemia

- Miliary, sized, red-Blue papules, Vesicles, Pustules, Hgic lesion → Crust → white scar & Brownish pig. (PLEVA like).

Tuberculids (Eruptive TB)

- **Def**: Cutaneous Eruption Caused by Hypersensitivity reaction to TB bacilli or their products (Ags) affecting patient ē Good CMI d.t Hematogenous dissemination of ↗

- **NB**: patients with Tuberculids are in relatively good health & Show:
  1. +ve Tuberculin Test. (Good CMI).
  2. Evidence of TB focus (usually inactive) Elsewhere.
  3. -ve staining & Culture for pathogenic Myco-bacteria in the lesions. (but PCR ±ve)
  4. Skin lesions Heal either Spontaneously or ē ## of TB
  5. Tuberculoid Granuloma ēout Caseation.

- **Etiology**: (1) **Old theory**: Hypersensitivity reaction to remote site of TB inf. (against bact. Ags)

  (2) **Recent**: Hematogenous dissemination of Bacilli to skin → rapid destruction by Good CMI (PCR Detect TB DNA in papular & Nodular Types only)

- **Types**:
  1. Lichen Scrofulosorum (Micropapular)
  2. papulonecrotic Tuberculid (Commonest type) (Papules)
  3. Erythema Induratum of Bazin's (Nodular)

Children & Young Adult

1. Lichen Scrofulosorum

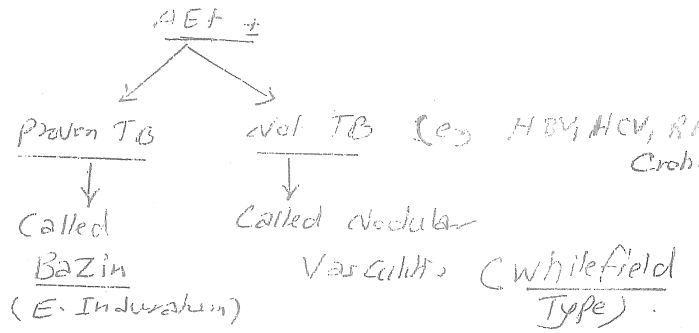
- Bilat., Symm., Asympt., grouped ~ peri follicular, Lichenoid Papules ē Exacerbation & Remission → No Scars.
- at Trunk
- **Hp**: peri follicular Tuberculoid Granuloma – No Bacilli No Caseation
- **DD**: All follicular disorders – L.P, L-Nitidus, K.Pilaris
  - Sarcoid, S, Id. reacts.

2. papulonecrotic Tuberculid (♀>♂) (PLEVA like)

- Asympt., Bilat., Symm.
- Dusky red, papules or papulopustules ē Central Necrosis → "Pox like Scars"
- at Extensor Extremities.
- **Hp**: Tuberculoid Granuloma Lcv.+
- **DD**: PLEVA & Prurigo

3. Erythema Induratum (Bazin's dis) [Nodular Vasculitis]

Def: lobular Panniculitis ⓔ Vasculitis.



- **CIP:**
  - ♀, obese, 40 yrs.
  - Winter → Exacerbation
  - Erythem- Violaceous, SC Nodules & plaques at ← Calve, Thigh, Buttock
  - → Involution or break down with → Irregular deep ulcers with undermined blush borders → "Atrophic (Hyperpigmented Scars)".

- **Path.**
  - Panniculitis (Mostly Lobular)
  - \+
  - Vasculitis

EN

- Septal Panniculitis
- Without vasculitis
- Pretibial
- No ulceration
- Et- ± TB, but HSV, Sty, Ht, Antimalarial

- **DD:** EN, PAN, Lupus panniculitis, S.C Panniculitis Like TCL & Perniosis.

(Ht) ← Anti TB / KI

NB

- EN (Mostly septal panniculitis ≠ vasculitis)
- LMDF
- Lichenoid tuberculid
- Rosacea (granulomatous)

→ No longer considered as Tuberculids.

* BCG inoculation (Ulcer)

Ht of Tuberculids: (1) Anti TB drugs (Rifampicin, Isoniazid, Streptomycin)

(2) others antibiotics

(3) plasm rest & Non specific measures.

Diagnosis of TB cutis

Absolute criteria : (3) [C]

1. +ve culture on Lowenstein-Jensen's medium of M. tuberculosis from the lesion.
2. Guinea pig inoculation.
3. PCR

Relative "unreliable" criteria : (6)

1. Clinical history & signs.
2. Presence of active proven TB focus elsewhere in the body.
3. Presence of acid-fast bacilli in the lesion itself.
4. Histopathology.
5. +ve reaction to tuberculin.
6. Effect of specific therapy.

Criteria for diagnosis of tuberculids :

1. +ve tuberculin test.
2. Evidence of TB elsewhere.
3. Tuberculoid granuloma on histological examination.
4. Good response to anti-tuberculous drugs.

NB . TB investigations :

1. AFB Staining & culture
2. Guinea Pig inoculation
3. Histopathology (HP)
4. Tuberculin test
5. PCR (Tissue) →
6. Interferon γ Release Assay (IGRA) (Blood)

(FDA-2005)

. Measurement of T cell IFN-γ response to Ags that are Highly-specific for M.TB & Absent from BCG & M. avium.

. 2 Types of this test :

(QFT-GIT) → (i) QuantiFERON-TB Gold In Tube test :

pt. Serum + 3 Ags → ELISA Assessment of IFN-γ level

(ii) T. SPOT-TB : 2 Ags + pt. Serum → Measuring The Number of IFNγ producing Cells.

- NB
  - QFT-GIT : IFNγ
  - T. SPOT.TB : IFNγ producing T-cells.

IGRA

(A) · Advantage :

(i). Sensitive > Tuberculin ((-Ve ē < BCG / M. Avium))

(ii). Single visit test (Tuberculosis ؟ يتعرف عليه بسرعة)

(B). disadv.

(i). Expensive

(ii). difficult

(iii). lack of prospective studies.

(iv) may be -ve in Early Inf. or False -ve ē M. marinum

· Tuberculin Skin Test (Tuberculin Mantoux Test).

· 5 units (0.1ml) of PPD $\xrightarrow{2-3\ days}$ (Induration) (Not Erythema)

> 10 mm in diameter → +ve Test. (doesn't differentiate bet. past & present Inf.)

· Interpretation

(1). The test is not Specific ; False +ve result: May occur ē BCG vaccination & MAIC Inf.

(2) False -ve results:

- Immunosuppressives
- Multibacillary Types of TB Inf.
- Sarcoidosis (saraidosis)
- Lymphoma
- Very Early Inf. (< 3-8 wks)

TABLE 6-2 FIRST-LINE ANTITUBERCULOUS AGENTS AND MAJOR SIDE EFFECTS

Drug	Side Effect	Special Comment
Isoniazid	Peripheral neuritis	From pyridoxine deficiency (+++ Pyridoxine 10mg/d)
	Hepatitis	Occurs with 1–2% increased risk with age >35
Rifampin	Hepatitis	
	Orange stain of secretions	May permanently stain contact lenses
Pyrazinamide	Hyperuricemia, Hepatitis	May precipitate gout
Ethambutol	Optic neuritis	Avoid in children under age 13
Streptomycin	Vestibular toxicity / Hearing impairment	Most common in elderly

Visual Acuity ↑ Green Color Perception Testing.

(Ch 8) Cut. TB

"كلهم ياخدوا على معدة فاضية" جرعة واحدة يومياً

- Drugs used:

- Isoniazid (INH): أقوى واحد (C)
  - 300 mg Id for adults
  - 6 mg/Kg/d For Children

- Rifampicine: (C)
  - Children: 20 mg/Kg/d.
  - Adult < 50 kg: 450 mg/d
  - " > 50 kg: 600 mg/d.

HIV & TB
- 500 Times ↑ risk in early
- Rifampicin Not given ∵ Protease inhibitor.

- Pyrazinamide: (C)
  - < 50 Kg → 1.5 g/d
  - 50-75 Kg → 2 g/d
  - > 75 Kg → 2.5 g/d.

Vit D2 (Calciferol)
150000 IU For 5dls → ++ Fibroblast → Strengthening TB.

- Ethambutol: 15 mg/Kg/ (C)

- Streptomycin: 0.75 gm IM/d.
- Paramino salicylic acid: 10 gm/d.

Bedaquiline (Sirturo)®
- - ATP synthase of MTB

أدوية جديدة لعلاج FDA (2015)

- Regimen: 4 X 2 / 2 X 4 (أشهر)

① Intensive = Initial phase

- 4 drugs For 2 ms
  - INH
  - Rifamp.
  - pyrizinamide
  - + either → Ethambutol or Streptomycin

(Initial Empiric) يتعطى لأي مريض أول ما نشخص بالـ TB. ويبقى كده لحد ما يجيب النتيجة من طريقة الزرعة وبتشيل واحد من آخر اتنين

Continuation phase

- (2) drugs For (4) months.
  - (INH & Rifamp.)

لو Resistant لـ INH
- pyrizin.
- Ethambu.

هاخلي بعض بدل ما يموت

DoT

(Directly observed Therapy)

لضمان إن المريض ما بيعملش Resistance لأنه بيبلع العلاج قدام حد بيشوفه عشان كده بنسميها DoT وليها ٣ أشكال

- DoT ← بيقف قدام المريض
- Daily ← المريض بيتعالج لوحده

Atypical Mycobacteriosis (Environmental Mycobact). (Non Tuberculous Mycobact)

- Why called Atypical Mycobact ??

- Not as TB & M. lepraе because:

1. present freely in the environment (ubiquitous) as: Water, Soil & animals.
2. Not always pathogenic (low virulence)
3. Not transmitted from Person to persons (but from ! environment (by) Inhalat° or Skin trauma) ← So better called [environmental Mycobact]
4. predisposing conditions must be present to produce inf. e.g obst. Pulm. dis, Trauma, Immunosupp. (HIV)
5. Poor response to Anti-TB drugs.

- Atypical Mycobact. include:

- 2 Lung → MAIC (Immunocompr.)
- 3 Skin ← Kansasii, Marinum, ulcerans, Chelonae/Abscessus → (N competent)

also called M.A. Complex (MAC)

- M. Avium-inter Cellulare
- M. Kansasii
- M. Marinum (Commonest Type)
- M. ulcerans
- M. chelonae / abscessus. etc.

• Primarily Cause Lung dis. similar To TB

→ Cause Skin inf.

* Cut. infection usually inform of ulcerated Nodule. (Indolent ulcer, Nodule or plaque) : توقعها لو لقيت .

(اللي بيطلع كدرام بيكون)

MAC

: Commonest Non TB Mycobact. infection in HIV patients (occurs Late when there is marked ↓ CD4+ while TB less frequent & occur Early)

- General manif. + Pulmonary affection ± Skin
  - Fever, Wt loss
  - Fatigue, L.N
  - (1) purulent Ingt ulcers
  - (2) papulo-pustules
  - (3) S.C Nodules

M. Kansasii

- 2nd Most Common Type
- usually affects patients ē HIV or CopD
- C/P: 1. General Manifs.
  2. Pulmonary: TB like
  3. Cut. (i) Sporotrichoid Nodules
     (ii) Verrucous "
     (iii) Papulopustules
     (iv) Cellulitis.

M. Marinum → Fish tank granuloma. (حبوب)

M. ulcerans → Buruli ulcer:

- Solitary Painless Sometimes Itchy Nodule (1-2 cm) after dur: 1-2 wks
- 1-2 m → Break down → Rapidly Spreading Shallow ulcer That may Involve upto SC
- Healing ē fibrosis → Joint Contracture.

M. fortuitum complex

- Present in Tap water, soil, dust.
- 3 Types: Chelonae (Abscessus), Fortuitum, Smegmatis
- may → Lung → Pneumonia (Hx: Heart)
  Eye → Keratitis, Endocarditis
  Joint
  Skin
- Bones, Nerves
- Commonest: Sporotrichoid S.C Nodules on distal Limbs
- Immunocompetent: localized Abscess Complications Traumatic injury (wounds, Abrasion, Catheter)
- Immunocompromised: Hx of Trauma (injury), disseminated Nodules, L-N, +ve Blood Culture

Treatment of cutaneous non-tuberculous mycobacterial infection

Micro organism	First Line	Other considerations
M chelonae	Clarithromycin + ciprofloxacin/doxycycline	Surgical debridement Dual antimicrobial therapy
M fortuitum	Amikacin + ciprofloxacin/doxycycline	Surgical debridement Dual antimicrobial therapy
M abscessus	Clarithromycin + amikacin/cefoxitin	Surgical debridement/excision
M marinum (بحري ٤-٣)	Ethambutol + rifampicin or doxycycline	Surgical debridement
M avium-intracellulare (سيتين)	Ethambutol + clarithromycin + rifampicin	Surgical excision
M. Kansasii (9-18 ms)	3-4 drugs For 18 ms.	
M. ulcerans	Antibiotics: Not effective; Surgical Excision → graft	

Fish Tank Granuloma

(Swimming pool Granuloma) → حمام السباحة الجرانولوما

Def: Cut. skin inf. caused by Atypical Mycobact. (M. Marinum) manifested as (localized granuloma) or Sporotrichoid Lymphangitis.

AEt: → M. Marinum: ch' by

- Non motile, Atypical AFB
- Grows in 2-3 wks on Lowenstein-Jensen Medium (at 32°C)
- They can produce:
  - yellow pigment on Exposure to light (photo-Chromogen → Runyon group 1)
  - Urease & Catalase

Route of Inf.: • Exposure of breaked or Abraded Skin

[Any Aquatic env. + Skin trauma]

TO M. Marinum (w) may be present in:

1. Aquarium (حوض السمك)
2. Salt water
3. Marina animals (Fish & Turtles)
4. Swimming Pools (rare): → المسبح العام

أي مرة تتعامل مع مياه أو أسماك

• So Risky patient are:

1. Fishermen
2. Fish Processing workers [الي بينظفوا السمك] → شغل
3. Salt water Aquarium personnel
4. Immunocompromised

Clp : . IP : 2-3 ws.

. The organism infect the skin through minor abrasions during dealing with infected water.

. lesion : . Papule or Nodule at site of Trauma (Commonest is Hand & Upper limb).

↓

Suppurate & ulcerate

±

- Sporotrichoid Pattern
- Deeper : JCT & Bone affect

. DDs : (1) Radiography : XR, CT, MRI → to detect deeper Invasion.

(2) Biopsy : ↓

Suppurative granuloma with AFB & No Caseats.

"ب"

. Treatment : For 3-4 m (or 1-2 m after disapp of SDs)

. deeper inf. → triple 2 m.

Tyra . Clarithromycin + Ethambutol

. others : Doxy . Mino, Fluoroquinolones, Septrin

. Resistant to : INH, Pyrizinamide & PAS.

Recently Thalidomide (Thalidomide derivative act by Immunomodulator).

Sporotrichoid diseases

(Sporotrichoid lymphocut. Inf.)

. Def. Inf. Cl By appearance of S.C. Nodules along dermal & lymphatic Vs.

. Clp early lesion start as Nodule (ulcerate) → distally at UL (Fingers or wrist) → irregular, linear Rough Spread along foam.

Et

. Sporotrichosis

. Atypical Mycobact. (Marinum)

. Leishmaniasis.

. Staph & Strept, Nocardia, Tularemia

. L.L & L.V.

. Fungal Histoplasmosis, cryptococcus

. Non Infectious : Lymphoma, LCH, M. Trans'l metastasis

Sarcoidosis

Def → Multi system granulomatous disorder ⓐ presence of wide spread, Non Caseating Epithelioid cell granulomas in > 1 system.

- **AET** → unknown but may be d.t:

Antigenic Insult in Genetically predisposed → **Immunological Reac** → **Granulomatous Reac**

↑ Incid of HA
- B 8,7
- DR 3
- DRB1

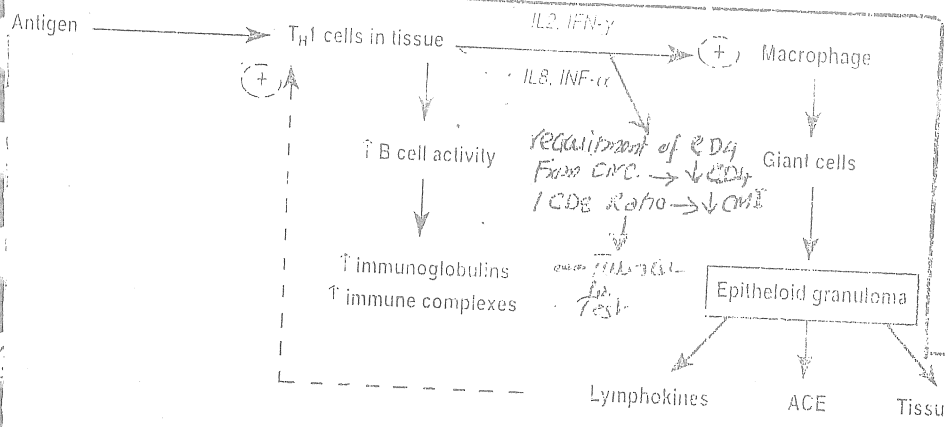
ⓐ may be

1. Infective
   - Mycobact. (M. TB, M. Avium, Para TB)
   - HSV-8
   - Propionibacteria
   - BCG vaccine
2. Chemical
   - ⓐ Beryllium
   - ⓑ Talc
   - ⓒ Pine Pollen
   - ⓓ Clay
3. Genetic
4. Environmental
5. Immunologic → ↓ HE, impaired CMI
   - ↓
   - Sarcoidosis

Immunological Abnormalities

↑ **Humoral Hypersensitivity**
- ⓐ ↑ Serum Igs.
- ⓑ ↑ Immune Complexes → ESR, Poly arthritis, Uveitis.

(↓↓) **Impaired CMI**
- evident by
  - ⓐ. weak < Tuberculin SKIN Trichophytin Dst
  - ⓑ. failed DNCB to induce contact sensitivity



The development of non-caseating granulomas is due to local presentation of an antigen by macrophages to T_H1 cells.

Ag+ → Th pass to site & dis → leaving behind (in serum) Anergic Suppressor T Cells

So < Tissue Th/Ts = 5 (N=1.8)
Blood 0.8 (N=1.8)

d.t ↑ Suppressor

Ass. dis ⊕ Sarcoidosis
- a). Thyrotoxicosis
- b). Cryptococcosis
- c). Vasculitis
- d). My Lymphoma
- e). Cancer (Lung)
- f). GM ENT

- Epidemiology:
  - Age: 20 - 40 y.
  - Sex: F : M = 1 : 2 (M > F)

C/P

- Any organ can be affected by sarcoidosis except the suprarenal gland.
- Usually start at the Lung or L.N of the Chest & then involve other organs:
  - Lung: 90%
  - Liver: 30 - 40%
  - Skin: 20 - 30%
  - Eye: 20 - 30%
  - Musculoskeletal: 2 - 35%

Note:
- Heart.
- Parotid.
- Kidney.
- Nervous

- So C/P of sarcoidosis is

Systemic → See above

Cut.
- Skin
- Mm
- Hair
- Nail.

* Cut. manif.:

(a) Incid. May occur in (25%) of cases of sarcoidosis & it the only affected by it in 25%.

(b) onset: →
- (in) 25% → Cut. manif. appear before system.
- 35% → systemic manif. before cut.
- 5% → simelataneous.

Cut. Sarcoidosis

- Specific (shows chic granuloma on Biopsy)
  - Classical Presentation
  - Clinical Varities
- Non Specific (Reactive changes)

Extra:
- EN (most common).
- EM
- Clubbing of fingers
- Calcinosis Cutis
- Ichthyosis
- Pruritus
- Discoid Ecz.
- General Symptoms: fever, chills, wt loss, Fatigue.

SKIN

Papular (miliary) Sarcoidosis (Common at Presentation):

Papules
- painless
- Color: skin colored, red-brown or violaceous, Hemispheric at first then flattening
- Surface: Variable scaling & umbilication
- Site: may be localized or Generalized
- Commonly: Bilat. & Symm.
  - face
    - eyelids
    - alae nasi
    - nasolabial
    - malar fold
    - Lips
  - neck
  - upper Trunk
  - & Extremities

- On Diascopy test: apple jelly Color. [Yellow-brown Spots]
- Fate
  - Coalescence → annular plaques
  - disappear → Pale, yellow or Telangiectatic

DD of Papular Sarcoidosis ?

- LMDF
- Granulomatous Rosacea.

Clinical Varieties = Great Imitator (Never vesicular / pustular)

- The lesion in Sarcoidosis instead of being papular It may be:

1. plaque (2nd commonest type)
2. Annular. (Central Clearing + peripheral ext. → Cic. Atrop)
3. S.C (Darier Roussy) Sarcoidosis: painless, Movable S.C Nodules +ve systemic effect
4. Angiolupoid (c Marked Telangiectasia).
5. Morphea form (c Marked Fibrosis)
6. Scar Sarcoidosis: on top of scar or old tatto → Infiltration irregular → Keloid like.
7. Lupus Pernio (Purpule Lupus).
   - Insedious onset of: Indolent, soft. doughy & Indurated, Purpule - dusky Violaceous nodules & plaques that affect areas Exposed to cold: Nose, Ear → at the Rim → (Notching), cheeks, Scalp, Fingers
   - Complication → Nose: Swelling, ulceration, Crusting → dyspnea.
   - → Fingers: Fusiform Swelling
   - → Scalp: Scarring Alopecia.

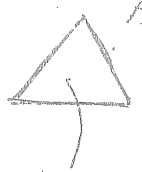
8. Hypopigmented infilt. Hypopigmented patches
9. ulcerative.
10. Erythrodermic & Ichthyosis, Psoriasiform

- What is the significance? "Lung"

Significant affection of:
- Lung: 75%
- URT: 50%
- Bone (Punched out granulomatous cysts): 43%
- ocular: 37%. (chr. uveitis)

- Mucosal Sarcoidosis.
  Pinhead sized papules ± grouped → plaques.
- Sarcoidosis of Hair: → Alopecia ± d.t
  - Plaques that Extend to scalp (annular)
    - Lupus pernio.
    - Macular lesions of scalp.
- Sarcoidosis of Nail: → Clubbing*
  → Subungual Hyperkeratosis.
  → onycholysis.

NB: childhood sarcoidosis, usually presented as



Less Commonly Lung affected
- less incid. of Lung.

Consider Sarcoidosis in any child complaining of Arthritis & eye affect.

Non Specific Cut. manif.

"مؤ" × EN
- Commonest non Specific Cut. manif.
- Similar to usual EN.
- may be part of Lofgren's Syndrome (triad)
  - Fever
  - Hilar L.N (BHL)
  - Arthritis (or Arthralgia)
  - Uveitis
  - EN

Is Sarcoid like EN ؟

"ش" its presence in Cases of Sarcoidosis.
↓ ??
Good Prognosis (80% chance of Resolution on 2 Ys).

- SC
- Lupus pernio

Systemic Sarcoidosis.

① Lung (90%) : • Stage I : → Bilat. HiPa, LN (BHL)
• Stage II : → as I + Parenchymal affect
• Stage III : as II + Infiltr. / Fibrosis / Pulm. insuff.

* Clinically : Cough, dyspnoea, Hoarseness, Nasal obst & Sinusitis. *

② Liver : Enlarged & ↑ Enzs. (Severe affection is rare).
"Pixi"

③ Renal : • Hypercalciuria >> Hypercalcemia → Nocturia, polyuria, polydipsia, Nephrocalcinosis, RF
"MC d.t : ↑ vit D synth. by granulomas
Histocytes → "Renal stones."

④ Musculoskeletal (more ↓ Lupus pernio).
(i). Joints → Polyarthritis
(ii). MS → DM (Dermatomyositis) like
(iii). Bone → Bony Cysts & Hand's & feet.
XX rarely US!

⑤ Eye : "KCS"
1. Uveitis (Granulomatous) (↓ Heerfordt's synd, Lofgrens synd & Lupus pernio)
2. Conjunctivitis
3. Kerato Conjunctivitis Sicca : (↓ Lacrimal sec. + parotid enlargement).
4. Eyelid oedema & Swelling : lymphatic obst.
5. Dacryostenosis
6. Proptosis.

⑥ Parotid Enlargment: (SS مع الـ MP مع الـ Uveitis)

Parotid
- Lacrimal
- Submand.
- Sublingual

[A] · Mikulicz Synd (KCS, SS) → B/Lat. involvement → Xerosis (dry eyes/mouth)

[B] · Heerfordt's Synd: (Uveoparotid fever)
- Fever
- Uveitis
- Parotitis
- Bell's palsy

· Bell's palsy:
- HZ
- Leprosy
- Sarcoidosis
- Melckerson-Synd.

⑦ Heart: HB, arrhythmia & death (Sarcoidosis of Heart is a leading cause of death (in Japanese).

⑧ Nervous: Granuloma of (Facial N. / optic N. / Spinal Cord) → Σ Palsy / Migrain.

Most Common is Cranial Neuropathy.

· Cause of death: Renal, Cardiac & Pulm. affect. Incid. 3%

Investigations of Sarcoidosis

كيفية التعامل مع أي حالة

Skin Invs
1. Biopsy.
2. Kveim Test.

Systemic Invs
1. CxR: Lung affect / L.N / Cardiac → Feet & Hand XR
2. Pulmonary function tests.
3. LFTs & RFTs
4. CBC: anemia d.t BM affect / Chr. Cor-Pulm / leukopenia, Thromb. cytopenia
5. Slit lamp Eye Exam.
6. Ca+: Hypercalcemia / Hypercalciuria

"Typ. Sg"
7. Markers of dis. activity (ACE)
8. Others: ↑ ESR, lymphopenia, ↑ Igs, ↑ CD4/CD8 > 3.5 = suggestive of Sarcoid.
9. ECG

· ACE ± TA (Tissue Biopsy)
- DM
- Alcohol.
- TB, Leprosy
- MAC

Histopathology (Reticulin stain)

علامة مرض تحت كوين

* Upper & Lower dermal, ** Non Caseating,

*** Naked **** Epithelioid cell granuloma or Tubercle.

* NB!
- L.V: upper dermal
- TT: lower dermal

** Not as TB
(No central Cheesy material)

*** Absent or Sparse Lymphoid cells
(by LM this → Lymphoid but:
by immunohistoch. → monocytes)

**** - Cells:
- Epithelioid cells.
- multinucleated Giant cells: usually Langhans Type (حدوة حصان)

Epithelioid cells may show

Schaumann Bodies
(Basophilic Mulberry like)
- Rounded, Laminated, Basophilic inclusions (Mulberry like) calcified.
- at first intra cellular then Extracellular.
- Represent: degenerating Lysosomes.

Asteroid Bodies
- Stellate, Eosinophilic inclusions
- Represent: Engulfed Collagen.

NB
Both are non Specific for Sarcodosis

NB

- Chicsy: L V Pathology (of L.V → atrophy)
  - upper dermal
  - scanty Caseation
  - Absent bacilli
  - Dense Mononuclear infil. (Cuffe Naked)
  - Epid. Changes → Atrophy, ulceration, Acanthosis, Pseudo epitheliomatous Hyperplasia.
- +ve → (Kveim test) / Tuberculin / Culture / Guinea pig inoculation
- (Stain) ZN

DD: of Tuberculoid Granuloma

DD: Similar histopathologic features are present in: TB, Tub. leprosy, deep fungal infections, beryllosis, cut. leishmaniasis.

- LV: The infiltrate is located close to epidermis, marked inflammatory reaction around and between the granulomas, more central necrosis and epidermis shows either atrophy, ulceration, acanthosis or pseudo-carcinomatous hyperplasia. Also, Kveim test, tuberculin test, tissue culture and guinea pig inoculation may be helpful.
- Tuberculoid leprosy: The granulomas follow nerves and therefore appear elongated and more central necrosis. (LTS)

	Lupus vulgaris	Tuberculoid leprosy	Sarcoidosis
Site	Upper dermis	Lower dermis	Upper & lower dermis
Shape	Rounded or oval	Elliptically elongated	Rounded
Adnexa	−	Involved	−
Caseation	±	−	−
Lymphocytes	+	+	−
Epidermis	Atrophy, Ulceration, Acanth, PEH	−	− / atrophy
Fibrosis	+ +	−	+
Special stain	ZN	Fite	Reticulin (Foch Stain)

(to stain Reticular fibres around granuloma)

- Foreign-body granuloma: polariscopic examination helps diagnosis.
- Acne rosacea resembles papular sarcoidosis but the infiltrate is perifollicular.

- Cold
- Sh
- Shd

Kveim test (Kveim Siltzback test):

- Intra dermal injection of Heat Sterilized suspension of Sarcoid tissue (from spleen of Infected Patient) → 2-3 wks → Papule that Enlarge gradually then Reach maximum size (4-6 wks = Highest activity of dis.)
- If No Papule: The area is excised for Histological Exam.
- This test is: +ve in: 60-80% of Cases of Sarc. / -ve in: Patients going to remission / False +ve: ≈ 2% (So this Quite Specific)..
- NB: Not done Nowdays d.t risk of Inf. after Tissue inje
- Markers of disease Activity:

  - Secreted by granuloma
    - Correlate with granuloma load
    - Specific & Sensitive (60%)
    - No prognostic Value
    - ACE (↑ activity → ↑ level.. also may ↑ in: TB, Leprosy, Silicosis, MAC)
    - ICAM-1
    - beta-2 microglobulins
    - Soluble IL-2 Receptors & TNF II Receptors
  - Collagenase
  - Fibronectin
  - Neopterin

Prognosis of Sarcoidosis:

- In General → Resolve without Relapse
- 20-30% → Some permanent lung damage.
- 10-15% → Ch. sarcoidosis that last for many yrs.
- 5-10% → Fatal if affect vital organs.

"ay" → 60% of cases of cut. sarcoidosis resolve without treatment in 1-2 yrs especially those patients with EN or with Löfgren's syndrome.

Tt of Cut. Sarcoidosis

Cdepend on ① Symptoms ② Severity ③ Progression ④ disfigurement

if

- Asympt., mild, Non progressive Non disfiguring
  - ↓
  - follow up for Spont. Resolution. (50% ⊕ in 1-2 yrs) - Sp. EN
- Sympt., Severe, Progressive disfiguring dis.
  - ↓
  - Corticosteroids

Cut. Sarcoidosis

- Localized
  - Topical Cs
  - intralesional Cs
  - intralesional Chloroquine
  - Topical Calcineurin inhibitors (Tacrolimus)
  - Surgical
  - Pulsed dye
  - Co2 Laser
- Generalized
  - [1] Low dose prednisolone (EOD Regimen)
  - [2] Other lines of Rx:
    - Antimalarial?
    - minocycline
    - Allopurinol
    - Retinoids
    - MTX
    - Thalidomide
    - PUVA
    - TNF α inhibitors (infliximab & adalimumab)
    - Cyclosporine
    - Levamisole
    - Colchicine

MTX + (Azathio / Tetra) + (PAT) (PUVA / Allopurinol / Thalidomide)

Systemic Sarcoidosis

- ↓
- Systemic Cs

1mg/kg/d prednisolone for 4-6 wks Taper over ms-ys as dictated by Systems affected

---

NB. Cs dose: 40mg/d for several wks → gradually ↓ to 15 mg EOD

. Lupus pernio: Cs + MTX or PDL ± Alefacept.

. Ocular Sarcoid: خطر يهدد الرؤية → Blindness.

Palisading Granulomas

* **Def.** → subtypes of Necrotizing Granulomas ch BY Central Zone of altered (degenerated) Collagen (Necrobiosis) surrounded by Histiocyte arranged in "Palisading Pattern"

- **Palisading** = spindle shapped Histiocytes (focally) Radiated (around) the *periphery (or) the long axis of the spindle shapped cells & their Spindle Nuclei are:
  - // to each other &
  - ⊥ to the central Necrotic area.

- **Palisading Granulomas are:** (2>0)
  - causes → [G. A (Granuloma annulare). ; A.G (Actinic Granuloma).]
  - 2 Necrobiotic [NBLD (necrobiosis Lipodica diabeticorum) ; NB.XG (Necrobiotic Xanthogranuloma).]
  - [Gout ; R.N. (Rheumatoid Nodules).]
  - [Cat scratch dis. ; Wegner's Granulomatosis ; Papulonecrotic tuberculide.]

- **NB:** Non Infectious Granulomas

  - Sarcoidosis
  - Palisading
  - LMDF
  - Granulomatous Rosacea.
  - FB Granuloma.

Granuloma Annulare
(Pseudorheumatoid Nodules)

Def: Chr. Idiopathic, self limited, Necrobiotic granuloma ch- by papules arranged in an annular or Arciform pattern.

- **Epidemiology**:
  - **Age**: usually (60%) < 30 yr.. ← Localized < 30 yr; Generalized < Peak 1st, Peak 30–60; S.C Nod → 2–10 yr.
  - **Sex**: M : F = 1 : 2 (F > M)

- **AET**: Unknown, but ± d.t delayed Hypersensitivity Reaction to unknown Ag ⓦ ± d.t
  - insect bite
  - Virus.
  - PUVA.
  - Sun Exposure.
  - Tuberculin test.

- **C/P of G.A** [No MM affect]

Classical presentation (localized GA)

lesion: multiple, flesh Colored (Pink Violaceous) papules arranged in an annular or arciform plaques (+++) (80%)

Site:
- dorsa of Hands & feet
- Elbows & Knees
- rare on other sites

Fate: (75% usually Resolve in 2 yrs but Recurrence occur in 40% (usually NO Scarring)

Clinical varities

- Localized (1–10 lesions)
- Generalized (>10 lesions)
- Subcut. nodular → Pseudo Rh. Nodule
- deep destructive.
- Patch (Erythematous Type)
- Perforating
- HIV ass.
- Neoplasm ass.
- Granuloma multiforme* (GM)

[Variety of its own kind]

Clinical Varieties

- **Generalized** < Age Bimodal < 10 yrs / 30–60 yrs.
  - Poor prognosis
  - ↑ Incid. ∃ Lipid abnormalities (eg) & DM
- **Subcut. Nodular**: (Pseudo Rheumatoid Nodules)
  - usally in children
  - S.C Nodules at < palm, Soles, Head, buttocks & Legs.
  - Look like Rheumatoid Nodules
- **Deep destructive**: may destroy underlying structures.
- **Patch (Erythematous)**: Patch < Erythematous, Infiltrated, non annular. (NF like or Morphea like).
- **Perforating**: Papules show central < umbilicated plug, Crusts. when squeezed → Little, clear, viscous fluid → heal → Pigmented Scar.
  - Represent: ! Transepidermal Elemination, Phenomenon.
  - ± ass. ē (HZ.) Scar (Wolf's Isotopic phenom.)
- **HIV associated**: at any stage.
- **Neoplasm** n: → ass ē Leukemia & Lymphoma
  - → Painful (rare!)
  - → unusuall location (Palms & Soles)
- **Granuloma multiform**: (Leiker) (Mkar dis.)
  - Limited to central africa.
  - more in ♀ > 40 yrs.
  - Affect Exposed sites.
  - DD: < TT, Syphilid
  - Pathology as: G.A (but) Prominent Multinucleated Giant cells.

Condition ass. ē G.A

- Appl.
  - DM → Type I = Juvenile
  - Hyperlipidem.
  - HIV
  - Neoplasm.
  - HZ (Scar)
  - Mauricas Synd. → GA, DM, Hepatomegaly, Dwarfism
  - NBLD
  - Sarcoidosis

• Mauricas Synd:
- GA
- DM
- Hepatomegaly
- Dwarfism

(Imp.) • DD (A) of Annular lesions
(B) of Palisading Granulomas

Pathology of G.A

Interstitial
Necrobiotic granuloma
Tuberculoid
(DD + ve Mucin + Eos)
→ (3 Pattern)

Granuloma

Interstitial pattern (70%) (Commonest)
(Infiltrative ~ Early Lesions)
- Seen in
  - some fully developed lesions
  - at edge of Lesions.

(i) Interstitial Histiocytes.
(ii) ↑ Mucin (Basophilic by Alcian Blue)
(iii) Intact. Collagen.

• Palisaded Granulomatous Pattern (Less common)
Seen in fully developed Lesions.

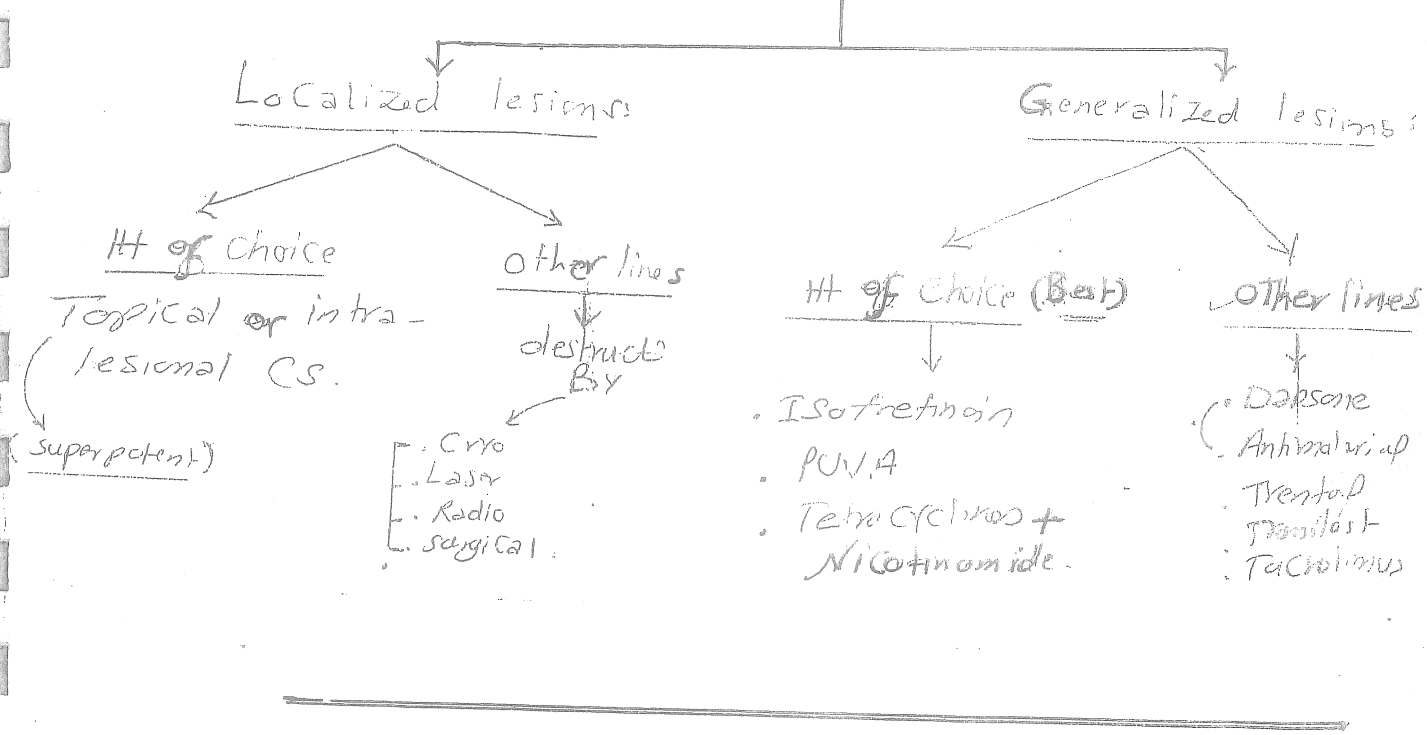
- Center
  1. Necrobiosis (altered collagen or degenerating)
  2. Mucin deposition
  3. Vascular Changes:
     - Fibrin
     - C3
     - IgM
     (BY Im. Flu.)
- Periphery
  - Palisaded Histiocytes
  - few inflam. cells (Eos)
  - cells of Giant cells

upper dermal

Tt of G.A

① Reassurance (No Tt): as Most Cases (75%) are self limiting ē in 2ys.

② For disfiguring cases:



Actinic Granuloma (AG)

(AEGCG = Annular Elastolytic Giant Cell Granuloma)

(Miescher's Granuloma of Face) (O'Brien's dis)

- Usually Female > 40 yrs.
- C/P: Annular plaques:
  - Asymptomatic
  - Border: Elevated & Erythematous
  - Center: slightly atrophic & Hypopigmented.
  - Site: Sunexposed Sp. < Head / Neck

- Pathology: 2 Varities

- Interstitial Pattern (common) → non palisaded (interstitial) granulomas ē FB Giant cells & Lymphocytes.

- Palisaded pattern (Rare)

(central zone → Elastolysis)

* NB: differs from GA in:

1. more FB Giant cell.
2. No Central Necrobiosis (but Central Elastolysis).
3. No Mucin.
4. No lipid.
5. Elastolysis (loss of elastic tissue in center of lesion)
6. Elastophagocytosis (elastic fibers seen inside Macrophages).

as GA ← 2, 3

as NBLD ← 4

Same as GA

Stain < Necrobiosis / Mucin

Special stains:

- Necrobiosis
- * Mucin
- FB + Elastic
- * +ve < Elastophagocytosis

NB: Elastic fibs stain "Verhoff Van Gieson"

Treatment

(i). Isotretinoin

(ii). Tetracyclines + Nicotinamide

(iii) PUVA.

Necrobiosis Lipoidica (NXBL)

- **Def.** Rare, Benign, necrobiotic disorder, affecting diabetics & prediabetics.

- **Epidemiology:**
  - **Age** < non diabetic: 20–40 y./ diabetic: 50–60 y.
  - **Sex:** M : F = 1 : 3 (F > M)

- **Aetiology:** unKnown, but ± [illegible]
  1. Related to diabetic microangiopathy:
     - In one study → 171 patients of NXBL:
       - 60% → diabetic (type I)
       - 30% → prediabetic (High Risk ← abnl GTT / develop DM later)
       - 10% → No Risk & No FH. (No FH)
     - Incid: it affect 0.3% of diabetics (3–7/100)
  2. Immune Complex (Vasculitis) suggested by IgM & C_3 deposition in 50% of Cases.

- **Clp** → Early lesions start as dull red asymptomatic papules & plaques → slowly Expand & may Coalesce → "annular plaques".
  - **Center:** yellow-brown, atrophic + Telangiectasia.
  - **Edge:** Violaceous & may show Hyperkeratotic Plugs (Represent Transepidermal Elimination phenomenon).
  - Slowly progressive & Tend to heal ± scar.

Abiefs → Commonest site: Shin of Tibia but may also affect: (thigh, Hand, Feet) (as G.A) → Scalp → atrophic Patches

Pathology:
- affect all dermis & S.C.T
- Extend to
- Diffuse palisaded & interstitial Layered Tteres granulomatous dermatitis aligned // to skin surface. [palisading]
- Lipid deposit
- Superficial & deep perivascular Lymphocytic infilt.
- Epid. → NL (or) atrophic.

- depth →
- layered Tiers //
- Necrob. ++
- Lipid.
- plasma cells.

[+++ < NB regions, Vascular changes, no mucin changes]

NB: this palisaded granuloma as G.A but differs in;

1. Granuloma is
   - Larger
   - more diffuse
   - more deep (deep derm. & S.C.T)
   - Horizontal Tiers.
   - Necrobiosis.
2. More marked
   - → Vascular changes (C3 from IgM)
   - → plasma cells *
3. Lipid deposition (oil Red O stain & scarlet Red stain)
4. No Mucin.

- +ve, lipid
- -ve: Mucin.

Treatment

1. Control D.M (usually no significant effect)
2. Cs → Topical: for Early lesion.
   → ILs: for active Border.
3. Excision & grafting.
4. Aspirin

• Necrobiotic Xantho-Granuloma (NB-XG)

(Class II Histiocytosis)

• Def → Multi systemic dis. ch by:

- • Cut. manifs:
- • Systemic manifs.

① Periorbital: Xanthelasma like plaques & Nodules (orange / yellow)

but ⟨ deep / Firm / indurated → may extend to the orbit → Eye ⟨ iritis, uveitis ✓ / Ectropion ✓ / Proptosis ✓

- dysproteinemia (IgG monoclonal)
- dyslipidemia
- Leukemia
- Lymphoma
- LN
- HSM

② Trunk & proximal Extrem:

orange → red, plaques ⟨ active border. / atrophic center ± Telangiect.

That → may ulcerate.

③ ± Acral Nodules.

• Histopathology: 1. Necrobiosis = Extensive

2. Palisading Granuloma ± foamy & Touton-Giant Cells. ↑ay

3. Cholesterol clefts ↑ay

4. Extracellular lipid deposits.

(Rx) → Directed to Paraproteinemia:

- Cs ✓
- IFNα-2b (3-6 MU ✗ 3/w)
- Eye radiation
- Nitrogen Mustard

Cat. Scratch dis

- Cat bite/Scratch $\xrightarrow{3-30d}$ Crusted papule or Nodule (± ulcerat)
$\xrightarrow{3-12\ w}$ Subacute Regional L.N (± suppurate) $\xrightarrow{2-6\ y..}$ Resolut^

- Etiology: ± chlamydia

- Ttt: (1) Antibiotics → Not effective (2) Cs: Control Sympts. & relief L.N

Gout

- disorder of Purine Metabolism ch by:

- ↑UA
↓
↑ deposit in (M) SKm, cartilage, Bmap, joint..

- Hyperuricemia.
- Recurrent arthritis
- urate deposition in Cartilage & SC in (Tophi) (aff. Ear Rim Exp)
- Renal dis.

Pathology

Urate Crystals surrounded by palisaded Histiocytes & mononuclear cells.

Wegner's Granulomatosis

(See vasculitis)

Granulomatous Respiratory Tract destruct.

- focal or diffuse Glomerulitis

- necrotizing Vasculitis & Granulomas

usually oral ulcerat^ ± Nodules

(palisaded granulomas).

2017 Leprosy (Hansen's dis)

Def: Chr. infectious, granulomatous dis. primarily affecting the peripheral Nerves & Secondarily involving The skin & mm & Certain Other tissues (of URT)

Specially: Eyes, Testes, Bones, liver.

Cold Areas (35°C)

Nose, Testes, Early lobes

Sup. NS

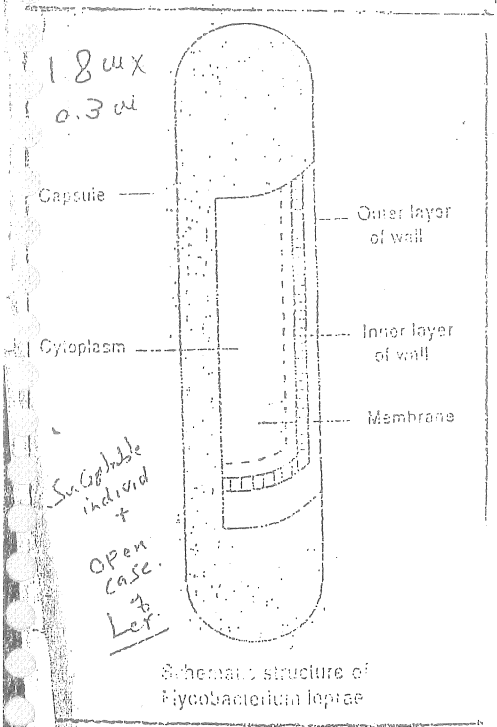
AE: Mycobacterium Leprae,

- obligate intracellular parasite of Macrophages & schwann cells
- Gram +ve, Acid fast & Alcohol fast but < Myco. TB.
- Non Culturable but can be inoculated in [Mice foot pads & Nine banded Armadilla.
- Stain: by Modified Ziehl-Neelsen (ZN)

Diagnosis: Stain, Culture

Structure

has capsule that is formed of 2 lipid layers



Schematic structure of Mycobacterium leprae

(1) phthiocerol dimycocerosate:
Non specific & shared by other organism.

(2) PGL: phenolic Glycolipid Coat:
- Specific for M. Leprae
- responsible for:

Binding to: G-domain of α chain of laminin 2 of basal lamina of Schwann cells

- difficult staining
- Foamy Macrophages

↳ It "Waxy Coat."

++TLR1 & TLR2 (on surface of Schwann).

Epidemiology: (2011)

- Age: Bimodal < Peak: 10 - 15 Ys. (Children are at greater risk)
  also at: 35 - 45 Ys
- Sex
  - Adults: LL > TL & M > F (2:1)
  - Children: TL > L-L & M = F
- Incid.: Tropical & subtropical areas.

M=F

Mode of infect^

* Requirments or Transmission:

1. Contagious Patient (open case = Multibacillary)
2. Close or Intimate Contact
3. Susceptable person [predisposing factors]

* Mode of Transmission:

Main mode: (droplets)
- Exit < Nasal or oral droplets (May remain viable on dried sec for 1-7 days)
- Entry < usually: Nasal mucosa or oral Mucosa
  less Common: breaked (Abraded) Skin

Less Common Modes:
- Eroded Skin
- Blood
- Faecoral
- Transplacental
- Breast Feeding.

IP: 3-5 Ys
(may ± short 1.5 Y or Long or 15 Ys)
(TL ≈ 4 Ys, L-L ≈ 10 Ys)

predisposing factors for development of inf.:

1. Genetic < HLA DR2&3 → TL
   HLA DQ1 → L.L
2. Endemicity
3. +Ve FH
4. Overcrowding
5. Poor Sanitation

Absence of these factors → usually No dis.

الوبئة - البلازل - بنجلادش
نيجيريا - فانيوب

Pathogenesis of Leprosy.

Most people Infected ē M. Leprae develops a "Subclinical infection" & recover Naturally & few people "who are susceptable" → develop the dis.

- Genetic
- Endemic
- FH
- Poor sanit & Crowding

M. leprae has predilection for "neural tissue" (Neurotropism)

It reaches the "peripheral" Nerves via: Endo & perineural BVS:

↓

Schwann cells (Target Organ)

- In Patients ē High Immunity (as proved by lepromine test) (TH1)

↓

++ Th1 (predominates)

↓

IL2, IFN-γ, TNF-β

↓

++ Macrophages (IL-12, TNFα)

↓

Efficient digestion & destruction of the bacilli

- The reaction remains localized to the Nerve (out spread to skin)

↓

Pure Neural leprosy

- The reaction spreads to the skin "only" [peri-neural]

↓

Epithelioid granuloma

↓

Tuberculoid Leprosy (TT)

- In Patients with Low Immunity (as proved by -ve test).

↓

-- Th1 (by the glycolipid coat)

↓

Th2 predominates

↓

IL 4, 5, 10, 13

↓

-- Macrophage

① Little Lymphocytic infiltration

② No Localization of inf. → Spread to skin & other organs (diffuse infiltration)

③ Bacilli Invade & Accumulate inside & outside the Macrophages

↓

Foam cells or Lepra cells

↓

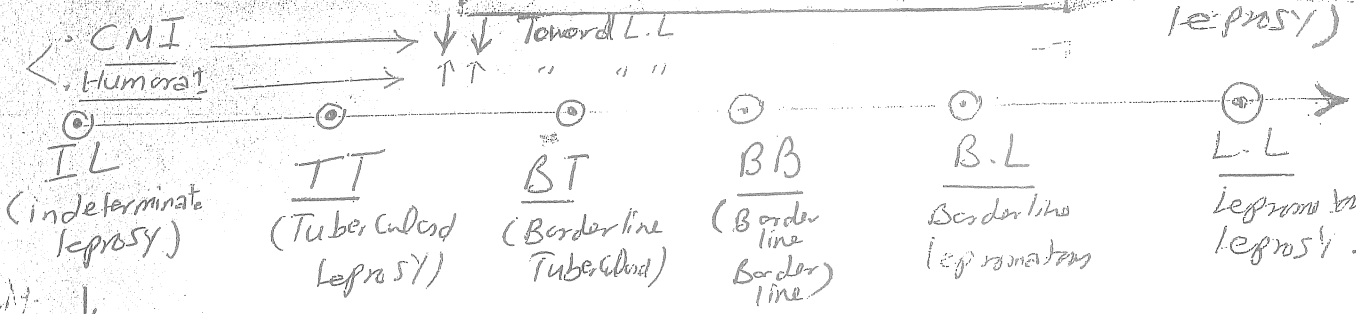
(Multibacillary

- In Both types No bacilli are detected (Paucibacillary leprosy).

• Classificat~ of Leprosy

I. Ridely & Jopling: clinical classificat~ (spectrum)
II. WHO classificat~: Therapeatic ~ (Paucl & Multi).

Ridely & Jopling classificat~ (Spectrum of leprosy)



early
⊙ Transitory stage in those ē undetermined Immunity.
⊙ May remains for (ms - ys) then either

- Resolve spont. (75%)
- progress To any Type. (weak Immunity).
  - if ↑↑ Lymphocytes → TT
  - if ↓ T Cells & ↑ Bacilli → L.L.

• We have 2 polar forms (stable)
TT
L.L (نفس درجة بكل للتان)

• the other forms < BT, BB, BL > unstable Types

May ē < good IH → go Towards TT L.L
Bad IH → go "

Indeterminate leprosy

- Early (initial), Transient, manif. of leprosy that occurs in patient ē undetermined Immunity
- usually affects children.
- C/P: single or few Hypochromic or Erythematous Macules usually ē NL Sensat~.
- HP: Non specific Inflamm. Infilt.
- Bacteriology: Few or No - Bacilli
- Immunology: Variable results of Lepromine test.
- Fate: see Above.
- TT: According to its progression.

	Tuberculoid Leprosy	Lepromatous leprosy.
CMI	• occurs in patient ē Very high Immunity	• occurs in Patients ✓ Very low Immunity (No Resistance).
Organs	• affect only Nerves & Skin!	• Can affect: Nerves, Skin, ex. mm, RES, Testes, Eye.
Infectivity	⊖ Non infectious (±)	⊕ infectious.
IP	• mean: 4 Ys.	• mean: 10 Ys.
Skin lesions	• Usually: Single or few (<5) & Asymmetrical. • usually: Plaque or patch But may be macular - single or few, Asym., erythematous or hypopigmented with well defined Elevated borders ē tendency to central clearing (Saucer right side up). ⊖ There are loss of: • Hair — dry, hairless • Sensat^ — Anaesth. • Sweat → usually affect: Face, limbs, Trunk, buttock • The Superficial nerve (sn) in the vicinity of lesion ± palpable. ⑤ Ear lobe infil. (Elongated segs)	• Multiple, Bilat., symmetrical without: loss of hair, " of Sweat, " Sensat^ • there are 3 types: ⓐ Macular: Multiple, Erythe. or Hypopigm., ill defined ⓑ Nodular: Skin colored, Pink or Coppery Papules ē smooth & shiny overlying skin. ⓒ Lucio type (diffuse) ⓓ Histoid Typ: NB L.L may → ① Leonine Face ② Madarosis: loss of outer ⅓ of Eyebrow ③ Ichthyosis of L.L ④ Saddle Nose. → any area can be affected (Folds, scalp) Except warm areas.

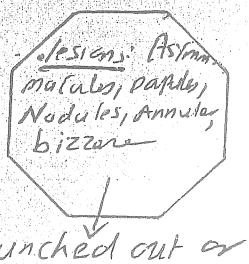
(N.B.) Earliest Manifs of L.L:
1- Skin & Nasal (stuffiness, discharge & epistaxis)

Epistaxis: نزيف من الأنف

	TT	LL
Nerve affect	• Nerve affection is: Early, Single • Confined to skin lesion & Peripheral NS	N. affection is: Late (3-4 s), multiple, Bilat. & Symm. • Not ass. c skin lesion
(i) Sensory (ii) Motor (iii) Autonomic → lost ← Hair, Sweat, Sebl.		
	• Manifs. of Nerve affect: → Sensory N. → dysthesia, paresthesia & hypoesthesia (Stocking & glove) → Neuropathic ulcers → Motor N. → ms weakness (foot drop & claw hands), wasting & Trophic changes → osteoporosis & Bone Resorpt. • Exam: thickened, Nodular & Tender.	
Other organ affect	• No affection to other organs.	• Affect other organ. • liver, spleen: Low • Kidney • Testes → orchitis → Gynecomastia, sterility • Eye → Lagophthalmos (N 7th), Corneal & Conj. anaesth. (5th) also in Uveitis, Iridocyclitis, Glaucoma • MM: Nasal ulcer, Epistaxis, Saddle Nose & Hoarseness. • oral: papules, Nodules at palate, Gum, Lips (palatal perforat.), Teeth falling
Histopathology	(Epithelioid Cell granuloma)	(Virchowcytic granuloma)
• Bacteriology (Skin smear)	-Ve (No Bacilli)	+Ve (Large No of bacilli)
Lepromine test:	Strong +Ve.	-Ve
• Immunology	• ✓ Good CMI. • ✓ Low HI (Low Antibody titer than LL)	• ↓↓ CMI • High HI (Antibodies detected in high titer but of no role cuz they can't attack Mtb cell in organism) + but HI: play role in Type II react°.
React°	• Usually No	• Usually occur.
Prognosis	← Good, Stable Course	← Poor, Liable to React°

Border line leprosy

- Immunologically unstable (either regress to TT or progress to L.L).
- No Systemic affect
- C/P, Bacteriology, HP, Lepromine test ~ TT & L.L بين



Punched out or Swiss cheese plaques (chic of BB).

	High Resistance	unstable resistance (dimorphic)			No Resistance
	TT	BT	BB	BL	LL
Lesions	1-3 (<5)	Few	Few or many & Asymm.	Many + Symm > Asymm	Numerous & Symm.
Bacilli smear	–	1+	2+	3+	4+
Lepromine test	3+	2+	+	+	–Ve
Histopath.	• Epithelioid cells decreasing → • Nerve destruction (Sarcoid like granuloma)			• ↑ histiocytes, foam cells, granuloma (Xanthoma like.)	

• Nerve affect in leprosy:

(i) Sensory Nerves: Most Commonly affected are UMRGSP (Ulnar, Median, Radial, Greater auricular, Superficial Peroneal, Lat. popliteal & Post. tibial).

ج. Why Ulner N. is the most Common

Sensation loss:
- Temp
- Light T.
- Pain
- Deep T.
- Pressure.

(i) prominent schwann (35°C)
(ii) superficial → Cool → suitable for M. Leprae.
(iii) over bony prominence → liable to trauma → devitalization of N. Tissue.

(ii) Motor Ns: rarely affected (deep → High temp).

(iii) Cranial Ns: 2, 5, 7 except olfactory (1). Trigeminal & facial.

• Special Types of Leprosy

1. Lucio Leprosy
2. Histoid Leprosy

• Lucio Leprosy (Pretty Leprosy = diffuse Lipromatosis)

- Type of L.L Thats Common in Mexico caused by M. Lepromatosis due to Total lack of Host Resistance.
- Ch BY ① Skin: diffuse dermal infiltration; so in old persons ē wrinkles on face → smoothout the wrinkles → youthful appearance (So Called Lepra bonito = pretty L.) (Scleroderma like)
  - ② Hair: loss of < Body, eye lash, ll Brow.
  - ③ Sensat.: wide spread loss.
  - ④ Nasal, Laryngeal affect & wide spread Telangiect.
- Has unique Reaction: Lucio phenomenon

• Histoid Leprosy

- special Type of L.L. ± occur < de novo or Relapse of L.L
- d.t < Discontinuation of tt (or) Drug Resistance (by) after chemo therapy.
  - d.t discontinuation or resistance
  - exists 2D
- Clp
  - Skin: DF like Copper or Yellow-Red dermal & S.C Nodules ē (NL) Skin over it. Common at — Face, lower back, Buttock.
  - Nerve → Abscess like Swellings. (Neural Histoid).
- Path: See before.

Pathology of Leprosy

3 Basic Histological patterns are seen

- **Tuberculoid Pattern (TT)** → dermal granuloma (Tuberculoid or Epithelioid)
- **Lepromatous pattern (L-L)** → diffuse infiet. of skin & other organs.
- **Borderline Pattern (BT, BB, BL)** → Patterns bet 1st & 2type

TT Pathology

↓

Dermal granuloma

- عليه → Elongated or linear. (Nerve. ليف عصبي)
- يحف → dermal along the Course of the nerve. (perineural) (حول)
- مكون من 1. Epithelioid Cells.
  2. Langhans Giant "
  3. Lymphocytes (at periphery < Large No. T4 > T8)
  4. Bacilli: Absent.
- Nerve → destruction

D-D from other Tuberculoid Granulomas (ex) Sarcodosis By Nerve in Flamm. & Fragmentat

(dermal)

Linear (Elongated), Perineural granuloma composed of ← (without) bacilli (ass. ب Nerve destruct)

(تابع المحاضرة)

L-L Pathology

- Skin → diffuse infiltration.
- SC → deep skin & other organs e.g Bone, Testes.
  - dermis
  - S.C.T

↓

Separating from the overlying epid. by well defined Grenz or Unna Zone (Zone of NL compressed Collagen).

- Cells: ① Virchow cells (Lepra cells or Foam cells)

Macrophage laden bacilli & Lipid droplets

Stain: H&E: → Foamy.
Sudan IV → lipid appear orange

② Plasma cells.

③ Lymphocytes < Scanty of T suppressor type (T8)

④ Bacilli: Numerous in dermis & have shape of: Isolated, globi, & granular (or) fragment (under HP) (Methinamine Silver)

- Nerve → Perineural concentric fibrosis (onion skin appearance).

Borderline Path

Mixed Virchow (LL) Tuberculoid (TT): بينهما

1) Some lesions show Virchow & others show Tuberculoid.
2) in Same lesion L.L pattern + T.T pattern
3) All lesions are Mix of foam cells & Epith. cells.

NB: in Histoid Variant Well circumscribed Prolif. of Spindle Cells containing bacilli that typically lie up along the Long axis of Cell. (Whorled arrangement).

NB on the Pathology

- Stain For 3
  1. Bacilli
  2. Nerve
  3. Lipid (Foamy cells)

- The most diagnostic features are:

① Presence of bacilli (AFB)

② Selective nerve destruction (by S-100 stain)

③ Perineural Concentric fibrosis.

Bacilli

- Fruitful sites (أكثر أماكن تجمعها)
  - Nerves
  - Subepid. Zone
  - Arrector pili m s.

- Stain:
  - Fite
  - H & E
  - Ziehl-Neelsen (أسهل وأوضح تلوين) → Bright Red
  - Fite
  - Wade

- Scarlet red:
  - Sudan III → Black
  - Sudan IV → Red
  - Methenamine silver → "detect fragmented bacilli"

- if scanty bacilli: before saying its -ve Take at least (6) sections.

+ Also Can be seen by PCR.

• Pathology of Border line patterns. (BT → BB → BL)

• Mix of both L-L (Virchow cells) + Tuberculoid form (granulomas) ... the predominance of the former versus the latter is dependent upon whether patient has BL, BB or BT

BT ⟶ BB ⟶ BL

* Virchow cells ⟶ تزيد في هذا الاتجاه
* Granulomas ⟶ تقل في هذا الاتجاه
(Epithelioid)

في وسط بينهما

① Some lesions are < as L-L & as TT

② Epithelioid & Virchow cells seen in same lesion

• Indeterminate Leprosy: difficult to be diagnosed Histologically only some lymphocytic infiltrate present (No < Foam cells granuloma).

Reactions in Leprosy

Def. Acute Episodes (Reactions) that may occur during the chronic course of Leprosy

- They may occur Either Spontaneous or ppt BY:
  - Initiation of TT (after 4-6 ms)
  - Stress
  - Inf.
  - Vaccination
  - operation
  - pregnancy
  - parturition.
- There are 3 types of Reactions
  1. Type I :→ Lepra reaction, (Reversal or down grading reactions.)
  2. Type II :→ ENL
  3. Type III : Lucio Phenomenon.

	Type I Reaction	Type II Reaction.
• Type of Leprosy	• Mostly Borderline Leprosy (BT, BB & BL) • Occasionally (rare): TT. (rare)	• Mostly: LL (in 80% cases) occasionally: BL (L-L & BL)
• Pathogenesis	• Type IV Hypersensitivity Reaction (change in CMI) • due to: (1) Initiation of TT (after 6ms) (up-grading (reverse)) (2) un Treated Patient (down grading) ~~(3) Spont. Purpersium~~	• Type III Hyper Sensitivity (Ag + Ig + C → deposit in Tissue, BVs & Lymphatics) • due to: (1). Initiation of TT (1Y) (2). Untreated Patient ~~(3) during HT~~.
C/P	Triad 1. Acute Neuritis 2. Acute Dermatitis. 3. Acral Edema	Triad 1. ENL 2. Systemic Manifs. 3. Constitutional M.

TT — Initiation / No TT discontinual → Lucio.] I & II Reaction

	Type I	Type II "only"
Skin manif. (Acute - Neuritis & dermatitis)	• ē upgrading: lesion of inflammat⁻ & ulceral⁻ • ē downgrading: progression of lesion Towards L-L (the NL skin remains Intact)	• Affect of NL skin (Existing lesions don't show clinical aggravat⁻). • There are: sudden onset of eruptⁿ of Evanescent (lasting for days) Erythematous, Dermal & S.C.T., Nodules ⓔ Generalized dist → ulcera • ENL: may be ↑ Vesicular, Bullous, Pustular (EN Necroticans), ulcerative; ↑ 1st manif ⓐ leprosy
Nerve	Rapid Nerve Inflamm. Acute Neuritis	• Slow Nerve Inflamm.
Associations	• Oedema of (Hands, Feet, Face) [↑ presenting S&S.] • Neuritis & paralysis (Hands, Feet, face (7th N.)) → (Facial palsy) (Acral Edema ⓐ Paralysis)	• Iritis • Iridocyclitis • Glaucoma • Arthritis • Myositis • Bone pain • Stridor • Glomerulonephritis • ↑ESR • Leucocytosis • ↑IgG, C2, C3 • Neutrophilia
Lepromine Test	• +ve in: upgrading reactions. • -ve in: downgrading "	No Effect
Histopath	• in upgrading shift to → tuberculoid pole • in downgrading " → Lepromatous pole	• LCV (Neutrophilic leucocytoclastic Vasculitis ⊕ scanty fragmented bacilli).
Treatment ⓒ Avoid pptd factors ⓡ continue ttt of Leprosy as usual. ③ Prophylactic Bcoing pregnancy during 1st 3m of ttt.	Prednisone 20-60 mg/d (tapered by 5mg/24wks for 24ms BT & 6ms BL) Other lines • Cyclosporine • Clofazimine (300 mg/d) 30	• Thalidomide (100-200 mg/d at night) Other lines • Cs (80 mg → rapid tapering) • Clofazimine (upto 300) • Pentoxifylline ± Clofazimine

NB

① • Type I Reaction: Cs ③ Lucio → Cs

② • Type II : Thalidomide

Lucio's phenomenon or Reaction

(Algol) (6)

- Type of Reaction that may occur in diffuse L.L (Lucio Leprosy) So, some consider it as atype of ENL.

- differs from ENL in: (5)

"discontinued Not initial"

1. initiated & stop of ## (Not & start)
2. No Systemic manifs.
3. No Neutrophilia or leukocytosis
4. ## → Cs
5. HP: LCV + dense Bacilli

- Clinically: ← with Vasculitis

  - Thrombosis & Necrotizing Vasculitis of Small Vs → Purpura, Hge, bullae → Painful Erosion → scar.
  - usually: below Knee, buttocks, forearms.
  - pathology → bacilli in skin & Necrotizing LCV

(##) → Cs

B Bacteridagical Exam.

• Skin Smear

(Slit smear = Bacilloscopy)

1. Routine in any suspected case
2. Highly specific but Not sensitive. (3٪) = "لازم" Can't detect Conc. < 10^4/g Tissue)
3. Value / diagnosis
   - Asses the Results
   - detect the most infectious ph
4. Technique: طريقة عمل (929)

- Sites = Common sites of L.L
  - 6 Routine sites + others
    - 2 Earlobes
    - 2 Elbows
    - 2 Knees
    - Forehead
    - Chin
    - Trunk
    - Buttocks
    - Extensor forearm ..

• Nasal Smear

(Not Routine)

Either By:

- Nose Blow Smears
- Nasal Scrappings → Not used ??

ع إصابع إيجابي ٧+ بيتفع ع كيس بلعوم وكلى.

Slit smear (طريقة عمل)

- lesion Cleaned ē Alcohol
- Fold is Picked up bet. thumb & Forefinger → squeezed tightly To render it free of blood.
- Small incision is made in dermis (L: 6 mm / depth: 3 mm) →
  - Turn the blade at right angle
  - Fluid (Serum) collected at the angle (Not blood) → Fixed (air dried Not flam.) & stained ē (Z.N) [Bacilli appears (red) rods over Blue back ground]
- Bacterial Index (BI): density of bacilli in Smear.
- Morphological index: "% of" "Persumable" living bacilli in relation to total No of bacilli in Smear.

Grading of BI (الكثافة)

* لازم ناخد بالنا إن أماكن الإصابة بتكون أماكن بتبقى فيها برودة شوية عشان الجراثيم تعيش فيها، زي L.L إيد وكوع وركبة.

(17)

Diagnostic clinical & Bact. Criteria

(Classification of Leprosy)

Bacilloscopy available (Slit smear)

- No bacilli → Paucibacillary L.
- +ve bacilli (even 1 bacillus) → multi bacillary L.

Bacilloscopy NOT Available

(Diagnosis in endemic areas)

→ WHO (1997)

[لو مفتش حالة . L وحبيت تشخص
[Lesions + عدّ ← لسرعة

- ≤ 5 Lesions → (PB) Paucibacillary
  - (SLPB) Single lesion → ROM therapy
  - 2-5 lesions → MDB for 6 ms
- >5 lesions → Multi bacillary (MB) → MDT for 2 yrs

[يبقى انت بتشخص حالة وعاجزها
ع دفاتر معددة]

Acc. To An Ethiopian Study

- If ≥ 1 of the following → Diagnosis of Leprosy:
  1. Hypopigmented or Reddish (Anaesthetic) patches
  2. Thickened Peripheral Nerves
  3. +ve Bacilli

So . Paucibacillary : is leprosy with < 5 lesions & no bacilli in smears & include TT . BT

- Multipacillary → ≥ 5 lesions with or without

B.B

كيفية قراءة الـ (Slit Smear) (using 100 OIF)

(A) BI = "Bacteriological index"

عدد البكتريا الكلي في كل عينة تم فحصها (OIF)

(B) MI = Morphological Index

نسبة البكتريا الحية الى العدد الكلي للبكتريا

1. Living = Solid
2. Granular & Fragmented = dead.

* With Rf : Bacilli disappear:

- BB : في الأول
- BL : 1-2 x
- L-L : 5-10 x

Grading of BI		
6+	=	>1000 bacilli per OIF
5+	=	100-1000 bacilli per OIF
4+	=	10-100 bacilli per OIF
3+	=	1-10 bacilli per OIF (in each OIF)
2+	=	1-10 bacilli per $\frac{10}{OIF}$ (10 Fields)
1+	=	1-10 bacilli per $\frac{100}{OIF}$ (in two OIF)
0	=	No bacilli in 100 OIF

آخر مكان تكثر فيه Bacilli هو ↓ dorsum of Hand.

NB

Bacilli present in	
100%	L-L
75%	BB
5%	BTF
0%	TT

C Histological Exam.: (Biopsy)

Skin Biopsy

- Site:
  - deep (to SCT)
  - From active Edge.
- → "Fite-Faraco"

Nerve Biopsy

- done if there is No Cut. lesions (Pure Neural leprsy)
- taken from Sensory N. (No risk of motor damage)
- e.g Super-facial peroneal @ fibular Fost.

D Clinical tests: (May aid in Dx; less frequently used Nowadays)

1. Lepromine test
2. Histamine test
3. Pilocarpine test

1. Lepromine test:

- Lepromine: is a "Crude Semi-Standarized preparation" of bacilli derived from a Lepromatous Nodule @ Fom Infected armadillo liver. (Heat Killed M. lepraе)
- 0.1 ml Lepromine Intradermal injection & Examinat is done either after
  - 48 hrs: → Fernandez reaction.
  - 3–4 wks: → Mitsuda reaction.
- If Nodule at site of inj. → +ve test.

• +Ve Lepromin test

• +Ve Fernandez reaction (Diagnostic)

↓

Indicate: delayed hypersensitivity reaction to: M. Leprae antigens or across reacting Mycobacteria.

NB:

- This test doesn't indicate Past or present Leprosy Inf.
- The test is:
  - (i). Strong Positive → in TT
  - (ii). Weak +ve → BT
  - (iii). -ve → BB, BL & LL.

• +Ve Mitsuda reaction. (prognostic)

- **+ve**
  - means that the patient can have good CMI to resist the inf. (TT & BT)
- **-ve**
  - Patient or populations at risk of Leprosy. (L-L & BL)

NB « Patients ê LL Never Became Lepromine +Ve Even when Healed »

Interpretation of Mitsuda reaction

- Nothing: -ve.
- ≤ 3 mm papule: ± (doubtful).
- 4-6 mm papule: +
- 7-10 mm papule; ++
- ≥ 10 mm nodule or ulceration irrespective of size: +++

– 1 2 3 4

4+ 3 2 1 – Nil

Histamine test (to detect Nerve damage)

(Sympathetic Assessment)

- NLLY: Histamine ID inject → ++ Nerves → Flare (local axon reflex).

- Result ± ← NL Response: L.L (late Nerve affect)
  - Absent " : TT (SW) (early)
  - Weak or delayed: BB or Indeterminat Leprosy.

Sweat function Test (pilocarpine test):

- Methachdine Test
- (Parasympathomimetic)

- Apply Tr. Iodine to NL skin (control) & suspected lesion → then inject pilocarpine → then apply starch to these areas (will turn blue if +ve sweating).
- Significance (only in non L.L) Why ??
  1. used in children in whom sensation can't be determined certainly
  2. Loss of sweating may precede Anaesthesia
  3. Blacks (Flare Not seen by Histamine test)

Serodiagnosis:

(1) Antibodies to M. lepra Ags: highest in LL & lowest in TT (عنوانين تقل)

(2) ELIZA: for detection of Antibodies against the phenolic glycolipid Coat (PGL)
- highest in LL & BL
- Low in TT
- ↓ during chemotherapy.
- ⊙ Useful screening test.

(Useful screening.)

(3) FLA-Abs: Fluorescent leprosy antibody Absorpt° test for detection of M. Leprae specific Abs.

(4) RIA: for Antibodies to Cell wall Ag ⊙ of M. lepra.

(5) PCR: for detection of M. lepra DNA but not helpful to detect mild & early inf.

(Mild & early)

(65) Leprosy in 3 situations

(5)

- Children
- pregnancy
- HIV patients.

Leprosy in children ch BY:

(i) Children are at higher risk to develop inf from the family Infected ē Leprosy.

(ii) usually Paucibacillary ē Single lesion localized To face or buttock

(iii) Good prognosis ē ≥ 75% Spont. Resolu

(iv) React is uncommon.

(v) Dapsone: 1-2 mg/kg/d

Rifampicin: 10-20 mg/kg/d

Clofazimine: 1 mg/kg/d.

(vi) Short IP

Leprosy & pregnancy

- Effect of pregnancy on leprosy
  1. Exacerbat
  2. Reactivat
  3. Reaction.

- Drug: 1. MDT: all (3) are category (C)
  2. Minocycline (D)
  3. Thalidomide (X)
  4. ofloxacin (C)

سؤال امتحان

Diagnosis of Leprosy.

(1) Clinical Examinat~ (Skin, Nerve, Diagnostic Criteria)

(2) Bacteriological Exam. (Slit & Nasal Smear)

(3) Histopathological N (Skin & Nerve Biopsy)

(4) Clinical Tests (Lepromine, Histamine & Sweat Funct~ Test).

(5) Serological Tests (ELISA For detect~ of PGL 2bs & PCR).

أهم ٣ :
- SSS
- Biopsy
- PCR

A: Clinical Examinat:

- Skin Exam. ← (Lesion, Hair, Sensat~)
- Nerve Exam.

lesion → Viewed / in good light, Directly & obliquely

For Hair →

For Sweating

Sensat~ → تحس كل واحد لحاله "لمس خفيف"

- Note TLPD (Temp – Light Touch → Pain → deep Touch)

2 lesions, Distal Extremities

- Examine the nerve for:
  1. Tenderness
  2. Consistency
  3. Size
  4. Symmetry
- Affected Ns may be:
  - Cord like (Thickened)
  - beaded
  - Abscessed.
  - Tender
- (i). Ulnar N: → Palpate at inner side of Elbow (when Elbow semi flexed)
- (ii) Median → at "wrist" when semi flexed.
- (iii) Greater auricular: → head turned to opposite side.
- (iv) Lat. popliteal: behind neck of fibula (E) Knee semi flexed.

* Most healthy show palpable Ns; so examine for Both sides ∑ for tenderness.

بـ استخدام قطعة أو دبوس وحاجة ناشفة أو باردة

بشرح إلو اختيار للمريض وبدوجه على أدلة لما يبقى عينه مفتوحة ولما يقفلها بنعلم وهو مقبض عينه ويقارن بين الـ NL Skin & lesion في جانبي الجسم.

• Treatment of Leprosy

- # of the dis.
- # of Reaction (نسبة)
- Others

- Chemotherapy (أهم واحد)
- 2. Immuno-therapy → "Vaccine"
- 3. Chemo-Immunoth.

(i) MDT
(ii) USA DT
(iii) NDT

"Multiple" or Multi- → MDT

• Chemotherapy "أهم واحدة تتذكرها"

① • WHO "بـ"

② USA "بتبع"

New Drug therapy
- Isoprodian
- Minocycline
- Fluoroquinolones
- Clarithromycin
- ROM

Chemotherapy: Aim:
1. Stop infect
2. ↓ Morbidity
3. Prevent Complications
4. Eradicate the dis.

- stopping & eradicate
- Prevent Complic & ↓ Morb.&

• MDT regimen is designed to avoid bacterial resistance

"بـ" • Dapsone:
- Most important drug.
- Cheapest
- Bacteriostatic.
- adult oral dose 100 mg/d (1-2 mg/Kg).

"ر" • Rifampacin.
- The most potent drug.
- Bactericidal
- dose: 10-20 mg/Kg od (600 mg on Empty stomach 1 day).

• Clofazimine
- Slowly bactericidal.
- anti-inflammatory
- Effective as Dapsone.
- 50 mg/d e Meals ⓪ a glass of milk.

Rif. is Rapid bactericidal while ... (Render the pt ... Rapidly).

MDT by WHO (Adults)

1. Paucibacillary (Single lesion) (SLPB) → ROM therapy (Single dose)
   - Rifampicine (600 mg)
   - oFloxacin (400 mg)
   - Minocycline (100 mg)

2. Paucibacillary (2-5 lesions): 2 drugs
   - daily Dapsone (100 mg at Home)
   - Monthly Rifamp. (600 mg under-Supervision).

3. Multibacillary (>5 lesions): 3 drugs
   - Daily (at home)
     - Dapsone
     - Lamprene (50 mg)
   - Monthly (supervised)
     - Rifamp. (600)
     - Lamprene (3...)

Durahon of tt

- Paucibacillary (2-5 lesions): For 6 ms & Follow For 2 Ys. (Relapse)
- Multi bacillary: For 1-2 Ys & Follow (observe) For 5 Ys.

NB USA Recommendation:

1. Paucibacillary: Dapsone & Rifamp. daily for 1 y.
2. Multi bacillary: Daily < Dap. Rif. Lamp. for 2 Ys.
3. No Recommendation for paucib. (Single lesion) → Most cases Resolve

- **Newdrug therapy**: aim of the use of these drugs:
  1. to over come the problem of Resistance.
  2. To Improve the patient compliance to (MDT) multi drug therapy.

- **Isoprodian**: contain mix of:
  - Dapsone (50mg)
  - INH (175mg) ✓
  - prothionamide (125 mg)

  tab =

  very effective
  - Dose: 15-30 Kg: 1 tab/d
    30-50 Kg: 2 tab/d
    >50 Kg: 3 tab/d.

- **Minocycline**
  - Very effective in dose of 100mg/d for 3ms
  - has bactericidal effect of all M. leprae

- **Fluoroquinolones**: (Pe 80/floxacin)
  400mg/d for 1-2 ms.
  Killing of M. leprae (99.9%) in multi-bacillary patients.

- **Clarithromycin**:
  500mg/d.

2. **Immuno therapy**:
   - IV peripheral blood Lymphocytes.
   - IV Transfer factor
   - Id Heat Killed "M. lepra Vaccine".

N.B

Child contact of L.L
Dapsone 25-75 mg/d every week.
or
Acidofasone inj 12ms For 3ys.

- **Other lines of ##**

(١) prevention & control
(٢) Patient Education (توعية المريض بالمرض)
(٣) ## Rehabilitation e.g physiotherapy for paralysis.
(٤) ## of Complicated N. damage.

(يتم استخدام الـ Reaction)

Thalidomide

2017

- Mechanism (3)

(1) Immunomodulating & Antinflammatory:

- Anti-TNFα. (أقوى مرة)
- ↓CMI: -- Thelper, -- IFNγ, -- IL12
- ↑HI: ++ IL4, IL5 (B Cell activates)
- ↑ T.reg.
- (Anti-Neubophil) (PG يكسر)
- Others: Anti- histamines, PG, A-Choline.

(2) Hypnosedative effect: pass BBB.

(3) Neural & Vascular Tissue effects — So: Teratogenic used in Cancer
- Antiangiogenic
- Anti Neurogenic (So → PN)

- Absorption: عالوجبة تقلل بالدهون. Peak Plasma. (2-6hr)
- Excretion: unknown. Non-Renal. half life: 9hrs.
- No: Relate to food, Renal Exc, CYP450 metab.

→ SE (إرجع تاني للميكانيزم)

(1) Teratogenicity:

- d.t Anti — Angiogenesis, Neurogenesis.
- 100% Specially at (21-36 w.)
- Phocomelia (limb defects — Absent / under-developm.) &
- عشان كده: ♀: 2 Methods of Contraception قبل الحمل بشهر... + ♂: لازم يلبس Condom + وسائل تانية

STEPS programs of: System For Thalidomide Educate & prescribing Safety
(1). Consent
(2). Educat packets.
(3) Monitoring.

- Pregn. (X)
- Lactate: No

• وسيلة حمل قبل بشهر - أثناء - قبل بيوم
• أثناء كل أسبوع لمدة شهر في كل شهر.

② P.N (20-50٪) → mild proximal ms. weakness + pp paraesthesia & Anaesthesia.

يشتكي من ضعف في العضلات القريبة أثناء الصعود.

. SNAP: Sensory Nerve Action Potential.

③ Sedation: drowsiness

ممكن يكون فيه بالليل وتزيد الجرعة تدريجيا

..Most Common S.E

④ Others: drowsiness, Xerostomia, Moode changes, ↑ Appetite, Brittle Nails, Edema & Xerosis.

. Thrombocytopenia
. leukopenia
. Erythroderma
. Thrombosis

لأنها تؤثر في أي خلايا تنقسم... (Cs or chemo)

C.I

• Absolute

. Hypersensitivity
. pregnancy ♂ ♀ & lactation
. preexisting PN.

• Relative

. Hepatic & renal Impairm.
. HTN
. HF
. Hypothyroidism..
. History of — Neurological disorders. Thrombosis.

Interaction

(1) - Not metabolized by Cyp450 Isoforms so Interactions of Importance are those with Additive Sedation (Alcohol, Barbiturate, Chlorpromazine)

(2) OCP: تؤثر بالتي السيتوكروم سواء كانت تثبط أو تنشط..

(3) PN inducing other drugs.

Follow up.

(1) يراقب: Pregnancy: إذا حبيا حمل قبل لعطاء بيوم ثم كل أسبوع لغاية ثم كل شهر.

PN: قبل وأثناء العلاج "SNAP"

(2) Nerve: ثم كل 3 أشهر - نفس الـ Neurological Exam.

(3) CBC — leukopenia / Thrombocytopenia

Indication & Dose.

(1). FDA → ENL (100-400mg/d)

(2). Other Responsive (Non FDA): يستعمل ↓ Sedation (because ... neuropathy).

. Nodular & Actinic prurigo

: PG, DLE, SCLE, SLE (Cupio for Response) (50-100)

CLOFAZIMINE

Drug properties: riminophenazine dye (red color)

Mechanism of action:(Antibacterial: Bacteriostatic and slow bactericidal & Antiinflammatory):
1- Disrupts cell membranes (activation of phospholipase A_2 leads to generation of membrane-destabilizing lysophospholipids);
2- Enhances superoxide production;
3- Inhibits neutrophil motility and lymphocyte proliferation

Dermatologic indications: treatment of multibacillary leprosy, other infections (mycobacterial, malacoplakia, rhinoscleroma) and inflammatory skin diseases including neutrophilic dermatoses (pyoderma gangrenosum, granuloma faciale, orofacial granulomatosis, erythema dyschromicum perstans and discoid LE

Dosage: 50–400 mg orally daily[*]; avoid long-term administration of >200 mg daily; (...اكتب طريقته وجرعته في leprosy).
In children:
- Should be given with food or with milk.

Side effects:
1- Discoloration of: skin (red to red–brown diffusely, bluish to violet–brown in lesional sites), hair occurs in 75-100% of and...cornea/conjunctiva and body fluids (urine, sweat, tears); It is reversible but may take several months to disappear after the end of treatment.
2-Xerosis and/ichthyosis;
3- GIT (abdominal pain, nausea, vomiting, diarrhea...the dosage should be reduced or the medication taken less often. Failure to do this may result in accumulation of clofazimine in tissues that can lead to blockage of the intestines..);
4-Ocular irritation;
5-Elevated Liver enzymes;
6-Cardiac arrhythmias (rarely; associated with electrolyte disturbances).

7- Side effects that occur rarely include:

- Dimness of vision: care required if driving or operating machinery.
- Dry, irritated eyes.
- Photosensitivity.
- Weight loss and loss of apetite.
- Depression, which may be due to skin discolouration.

Contraindications: prior hypersensitivity reaction

Pregnancy and lactation: should be avoided during pregnancy (category C, crosses the placenta, and skin discolouration has been seen in neonates.) and lactation (concentrated in breast milk)

Dapsone 2017 (BS)

Syn. → diamino-diphenyl sulfone

Mechanism of Action:

A. Antibacterial → -- dihydrofolic acid of the Bact. → stop its growth.
   - static
   - cidal

B. Anti-inflammatory: → -- Neutrophil Chemotaxis
   (so ## of choice in Neutrophilic dermatoses).

Preparations:

1. oral Tabs → 50 mg
2. Topical gel → (under trial).

Uses:

A. FDA approved
   - leprosy
   - DH
   - Use? → prevention of Pneumocystis Carinii Pn. in HIV pt.

B. Non FDA approved: (Neutrophilic dis):
   - Bullous:
     - Pemphigus family → IgA Pemph.
     - Pemphigoid " → (CP, DH, LAD, EBA, BSLE)
   - Eo:
     - PG
     - Behcet
     - sweet
     - Pust. Ps
     - GA
     - Vasculitis < LCV / EED
     - AV

Nodulo-cystic Acne.

Pharmacodynamics:

- Slow but Complete Abs. after oral intake
- widely distributed Except the Eye.
- Skin level is 10 times Serum level.
- doesn't cross the placenta but Excreted in milk.
- Metabolized by liver & Excreted in bile (10%)

SIDE EFFECTS OF DAPSONE

Red blood cell toxicity	• Hemolytic anemia • Methemoglobinemia
White blood cell toxicity	• Leukopenia • Agranulocytosis
Dapsone hypersensitivity syndrome (2-7 ws)	Hepatitis, lymphadenopathy, fatigue, anorexia, Erythroderma...
Cutaneous reactions	• Morbilliform eruption • Urticaria • Fixed drug eruption • Erythema nodosum • Exfoliative dermatitis • Stevens-Johnson syndrome • Toxic epidermal necrolysis • Phototoxicity • Drug-induced lupus erythematosus
Gastrointestinal manifestations*	• Anorexia, nausea • Hepatitis • Cholestatic jaundice • Severe hypoalbuminemia
Neurologic associations*	• Headache, dizziness • Peripheral neuropathy • Blurred vision, tinnitus • Insomnia • Psychosis

Dapsone Synd (6 wks Synd) IMN like

P.N

NB S.E on Blood → 2 RBCs, 2 WBCs.

Hemolytic Anemia

يتعرض مع كل المرضى لكن بعضهم يتأثرون بشكل أكثر

(d.t oxidizing effects of sulfones) → ↓ Reduced Glutathion.

- F. → G6PD efficient → Compensate
- F. → G6PD deficient → Can't

→ So G6PD assessment Both

→ Quantitative & Qualitative.

(أفضل شيء Comprehensive.)

Met hemoglobinemia

- Fe^{++} (Ferrous) in Hb
- ↓ Oxidized to
- Fe^{+++} (Ferric)
- ↓ Met Hb → Cyanosis, Breathlessness, angina.

(Can't carry O_2 or delivery O_2 To tissues)

→ يتعرض كل المرضى بشكل عادي بنسب متفاوتة [٥-١٠٪]

Cardio pulmonary manifs

→ "No problems"

Leucopenia & Agranulocytosis

(<2000)

may be manifested by:

1. Fever
2. Sore throat
3. Signs of Inf.

→ So

→ Stop Dapsone.

NB: Agranulocytosis in cid. TT in:

1. Elderly > 60
2. OH > leprosy (30 times)

How to avoid the Risk of Hemolysis.

(٤ طرق)

- dosing (100 mg/kg) & vit E (مضاد أكسدة)
- Pre tt assessment (مهم) of G6PD
  - Quantitative
  - Qualitative.
- Reticulocyte Count assessment (باستمرار أثناء العلاج)
- Dapsone test (مهم)

تعطى المريض قرص وتقول له فعل:

- كوب أو زجاجة
- في الصباح وقبل الإفطار
- احمرار مع البول

Pre HI & during HI
Follow up.

قبل العلاج ②

1. G6PD
2. LFTs
3. RFTs

NB البعض بيقيس:

Met Hb Reductase"
↓ acord
Met Hb.

أثناء العلاج ③

1. CBC
   - Reticulocytic Count
   - Agranulocytosis
2. LFTs
3. Neurological Exam

* كل أسبوع طبعاً
كل شهر طبعاً أيضاً
كل أسبوعين ممكن

كويس: ① تقليدي
Manual Tasks
② تليفون طرفين
مرايم

Any disturbance → Stop. HI.

Drug interaction:

- Probenicid → ↓ renal Exc.
- Rifampacin → ↓ serum halflife.
- phenacetin → ↑ RBCs toxicity
- PABA → Interfere Dapsone Act^

كويس
Antidote of Dapsone toxicity is IV Methylene Blue

Methotrexate:

↓ بيعوز إضافة فيتامين مجموعة B vit

(أيه العلاقة بينها)

- Contra indications:
  - deficient < G6PD & Met Hb
  - LFTs & RFTs Impairment
  - Anemia & leukopenia
  - Lactat^ (Excreted in MilK
  - Hypersensitivity

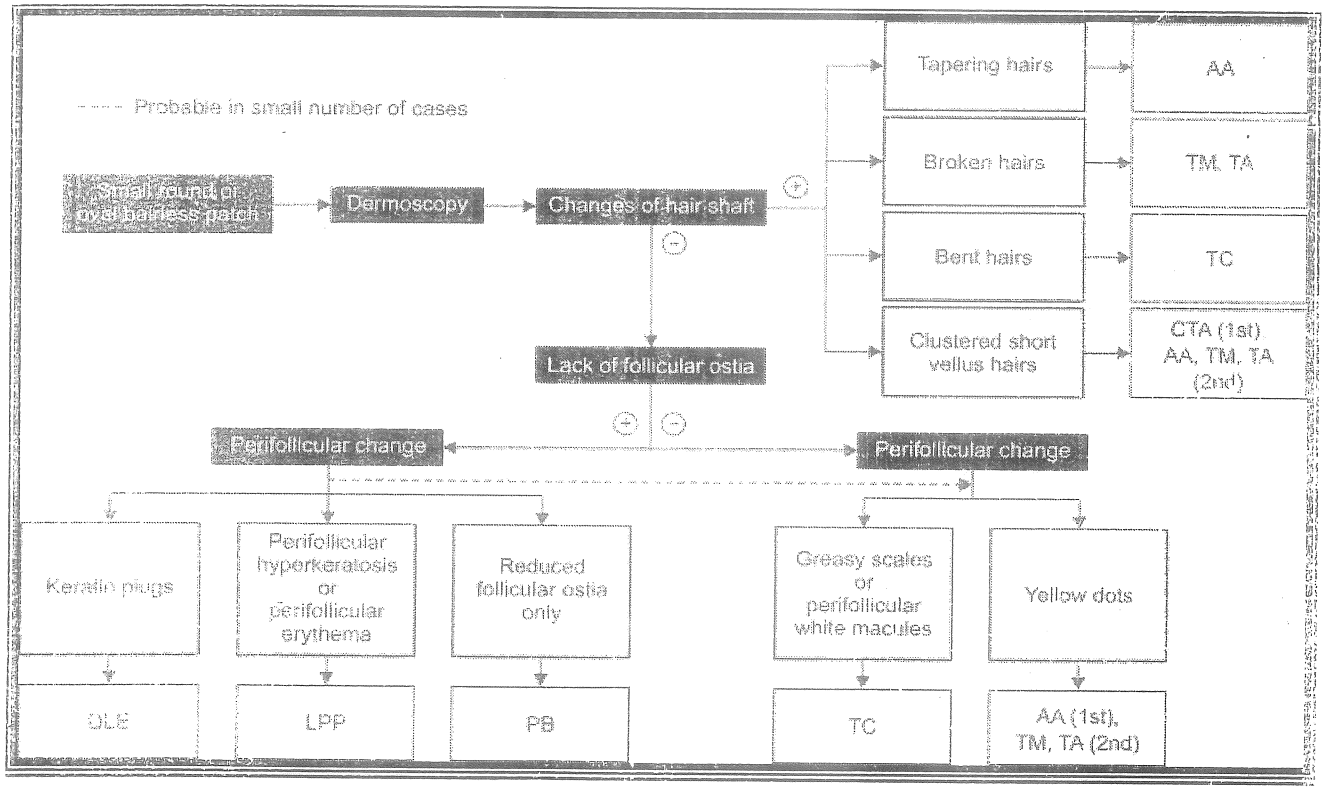
- Pregnancy: → Category C (can be given in leprosy)

- Some reports recorded Hemolytic anemia in fetus but Am. AC of Ped approved it (when indicated).

Dermoscopy of Hair Disorders

AGA	AA	Trichotillomania	LPP	DLE	Hair shaft disorders	Telogen effluvium	Tinea capitis
Hair shaft diameter variation of >20% hair shaft (earliest feature)	Yellow dots with short vellus, dystrophic and tapered hairs	Hair shafts of variable length	Peripilar casts	Atrophy	Monilethrix (beaded shaft)	Diagnosis of exclusion	Black dot tinea shows stubs of broken hair shafts with scaling
Peripilar halo in early stages	Black dots (cadaverized broken hairs)	Longitudinal splitting of hair shafts	Target pattern "blue-grey dots"	Complete follicular paucity	Trichorrhexis nodosa (brush fractures)	Decreased hair density with presence of empty follicles over the entire scalp area with no site predilection	Comma shaped stubs are a specific feature
Predominance of follicles bearing single hair	Trichogram shows dystrophic fractured and telogen roots	Coiled fractured hair shafts	Spared intervening follicles	Arborizing telengiectasia	Trichorrhexis invaginata (shaft nodes)		Blotchy pigmentation, erythema, scaling, pustules and follicular scale-crust formation are seen in inflammatory tinea capitis
Hypertrophy of sebaceous glands			Trichogram shows anagen roots	Hyperkeratotic follicular scales	Pilitorti (twisted shafts)		
			White dots				

AGA - Androgenetic alopecia, AA – Alopecia areata, LPP – Lichen planopilaris, DLE – Discoid lupus erythematosus



DH (Dermatitis Herpetiformis) (Duhring dis)

- **Associations:**
  - **I Common:**
    1. Gluten sensitivity enteropathy (GSE): Celiac dis (CD) (100%)
    2. Hashimoto Thyroiditis
    3. DM (Insulin dependant)
    4. Intestinal lymphoma
  - **II Rare:**
    - Addison
    - Alopecia
    - AICTDs
    - Sarcoidosis

Celiac disease (CD)

- **Def-** chr. GIT dis. ch By inability to Tolerate Gluten (GSE) (its active fract: gliadin ; in present in: Wheat, rye & barely)
- **Intestinal Mucosa:** 3 grades of affect:
  1. just infiltrat of Lamina propria by lymphocytes
  2. mild Villus atrophy
  3. " " "

- ① كل حالات الـ DH معاها CD بس مش كل الـ CD معاها DH
- ② ليه الـ CD بيظهر في الأطفال أعراضه بينما أعراض DH في الكبار (بسبب تكون IgA وتأثيرها)
- ③ ليه كتير من الحالات مش معاها أعراض CD (No Abdominal symptom) لأنه معظم تأثير الامعاء Mild

CIP (= No Mucosal affect)

Adulthood DH

- **Eruption:**
  - Polymorphic: Papules / Vesicles < Bullae ± Urticarial or Targetoid lesions
  - grouping (acr)
  - Bilat. Symm. on extensors:
    - 2 limbs.
    - shoulders.
    - buttocks.
    - Postaxillary Folds.
  - Severly itchy (Paroxysm)
  - Healing: scarring & Pigm.
- **Flaring:** usually e ingestion of Gluten (or) Iodide containing Food
- **Abdom. manifs:** ± Pain ± diarrhea, undernourishment.

Childhood DH

↓

as in adults

+

Palmar blisters or Brown macules.

NB

the chic findings

Spont Remission that lasting as long as (1w) that termination abruptly e New Crops.

Pathogenesis of DH

- Interact bet 3:

1. Genetics (وراثي) ← HLA DQ2 (90%) / HLA DQ8 (10%)
2. Environmental factors: Gluten & Iodides
3. Autoimmunity IgA autoabs.

Gliadin: is fraction of Gluten

TGs: enzymes in Tissues (TG2) use Gliadin as substrates

Gluten Containing diet e.g Wheats → passes to lamina propria of the Intestine.

e. GT_2

↓

Gliadin-TG2 Complex

↓

Formation of (Anti-TG2 IgA) autoantibodies

↓

Cross react with Epidermal TG3

↓

Formation of IgA-TG3 Immun-complexes

↓

deposition in dermal papillae (with) Neutrophil chemotaxis.

↓

Subepid. blisters (L.L)

Neutrophil Microabscesses (IgA → ++ C3a → ++ Neut.).

granular IgA deposition at dermal papillae. (NOT BMZ as in LAD)

Dapsone: -- Neutrophil accumulation

Iodides: ++ " "

• even if Topical Iodide Test To confirm ∅

Dapsone is ## of dis. of Neutrophils or IgA.

((N B))

يعني سلفيه وابسون ممنوع GFD، الدابسون وكمان GFD

- GFD = Gluten free diet

Dapsone يجب تجنب فول وبازيلاء

- Sulfasalazine: Category (B) in pregnancy.

- Dose : 1-2 gm/d

- Sulfapyridine : gm/d.

- S.E : Hypersensitivity.
  - Hemolytic anemia
  - Proteinuria
  - Nusea & Vomiting

لازم تشرب كتير مايه

- Sulphapyridines:
  - Sulphasalzine 1-2 gm/d
  - Sulphapyridine 2-6 gm.
  - Sulfamethoxypyridazine 0.5-1.5 gm/d.

- Path: → subepid (intra L.L) blisters ē Neutrophilic infilt.
  → Neutrophil microabscesses (in) dermal papillae.

Es. infilt is +ve So difficult to diff from BP. ↓ do (DIF)

- DIF: → 90% (granular) IgA in "Dermal papapillae" — hallmark
  (HL). NB: Granular + linear (5-10%) . Fibrillar: rare.
- IIF: → Usually −Ve (because IgA formed locally in skin)
- Circulating Abs: Anti TG2 (Endomysial), Anti TG3, Antigliadin & Anti-Reticul.
- Targeted Ag: → Transglutaminase → Tissue: TG2, Epid = TG3

---

(44)

Stop gluten & Iodine (Atkins diet) ↓ give

Value: 1. ↓ Gut & intest. manif.
2. ↓ Dapsone or (Stop it)
3. ↓ incid of Lymphoma.

Gluten: Wheat, & Rye
Oats, Rice, Corn

Dapsone or SulFapyridine

① 100-200 mg/d (± ↑ upto 400 /day — Hemolysis)
② dramatic Response ē in 48 hrs. (Therapeutic Test)
③ For 3-6 ms.

2-4 gm /d
Sulfasalazine 1.5-4 gm/d → metabolized To Sulfapyridine.

Sulfapy. ↓ → Colchicine, Tetracycline, Nicotinamide, Ciclosporin (but ± ↑ Lymphoma), Heparin

Cs → Systemic: No effect
→ Topical: ± ↓ itching

الأكلات "شفوي"

- Gluten Free:
  - الرز
  - الذرة
  - الفيرونة الطازجة
  - السكر
  - البطاطا
  - الفول الصويا
  - الخضروات والفاكهة الغير نشوية
  - البازلاء
  - الملح والفلفل
  - جوز الهند
  - السيكولاتة

- Gluten Containing:
  - قمح (الخبز)
  - شعير barley
  - جاودار (نوع من القمح) Rye
  - السيمولينة والسباجتي
  - المعلبات عادة وطبعاً
  - البيرة والشاي السريع
  - الآيس كريم

١٠

- Avoid Iodine Containing Food:
  - Iodized Salt
  - Fish & Shellfish.

Diagnosis of DH

1. Hpy: DIF & IIF
2. Genetic: HLA → DQ2 / DQ8
3. Intestinal Biopsy
4. Iodine & Dapsone Test.
5. Investigate for Associations.

بعض الأسئلة بتكون:

- IIF → -Ve because IgA Formed Locally & don't circulate

endomysium: CT that ensheaths the ms fiber.

LAD = linear IgA Dermatosis (LABD = linear IgA Bullous D)

. has 2 Age peaks :

(1) Childhood Type : . Called chronic Bullous dis. of childhood (CBDC)

. onset < 5 ys , Resolut ~ after 3-6

(2) Adult Type : ~ 60 ys.

(أكثر خطورة prognosis)

CP : . Itchy

. Vesicles & Bullae — clear or Hgic

. on — NL / Erythematous or urticarial → Skin

. Pattern : 1 "String of pearls / Beads" : Vesicles & Bullae are at the edge of Annular or Polycyclic Erythematous or urticarial plaques.

("عقد" (Crown of Jewels))

2 Discrete : BP like

3 Grouped : DH like

→ More ē Adult Type.

. Distribut :

1. Childhood Type : (Flexural)
   . lower abdomen , Anogenital & Perineum
   . Acrofacial & Perioral.
2. Adult Type : Trunk & L.L

LAD ē children called chronic Bullous dis. ē childhood (CBDC)

(مرادف انجليزي)

other Non classical lesions :

. Erythematous (Macules / papules / plaques)

. EM - like (Targetoid)

. Morbilliform.

. Cicatricial Variant : EBA or CP like (ē severe Mucosal affect)

- NB: Skin lesions are itchy & have Burning sensation (but < DH).

MM affection (≃50%)
- Common & ± Early sign.
- has Cp like picture. (Severe).
- Any Mucosal site ± affected.

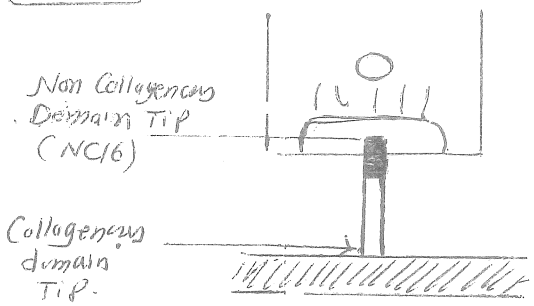
: الـ MM
- 50%
- early
- Severe
- Multiple
- Cp like

- Pathology → Non Specific DH or BP like Subepidermal Blisters & Neutrophilic Infilt. (DH Microabscesses like); ± with Eosinophils (BP like)..

- Path سبب & DIF

DH:
- granular IgA & Neut. at dermal papillae
- LAD: linear IgA & Neut at very tip.

(NB) on BP Ag2 / 180 KD / Collagen 17:



- BP Ag2 has 2 parts:
  1. intra Cellular Part → Not Target in Bullous dis.
  2. Extra Cellular ✓ → Targeted; has 2 parts:
     - (i) MCW1: أول جزء بنظهر فرانج إكليبر وبيكون "NC16 tip" الجزء
     - (ii) LABD97: Collagenous أو LD domain Tip. الجزء

- DIF: Linear IgA at (Not at D-papillae as in DH).
  - L.L (Mainly)
  - SLD (ass. ē Anchoring fibrils) (±)
- ± linear C3 & IgG (BP like).

- IIF: ≃ 50% IgA antibodies directed against.

(Ag)
- L.L ←
- LD → laminin.
- SLD -

- L.L antigens or:
  - 97 KD
  - 120 KD [Portions of Extra-Cellular domain of BP Ag2]
  - 285 KD [Ag in L.L] (LAD 285)
- LD: Laminin
- SLD (minority of cases) → Anti Coll 7 antibs. ("Anti-250 KD protein Abs ✓ D part from Coll 7A).

NB1: Conditions that may associate LABD:

- ulcerative Colitis (7%)
- Malignancy
- Drugs
- Gluten sensitivity (GSE). (Rare)

NB2: Types of LABD: (4 Main types):

1. Idiopathic (Classical) Type: 2 Age peaks
   - preschool (5yr)
   - 60 yr.
2. Malignant associated Type.
3. Drug induced: (جرعة بسيطة)
   - Most Common: Vancomycin (الأكثر)
   - less Common: ACEI, NSAIDs, penicillin & Cephalosporins, diclofenac
   - uncommon: phenytoin & sulfa.
   - rare: Ciclosporin, PUVA, Rifamp.

   ← 2 Ch
   - No MM
   - resolve after stop of drugs by 2-6 wks
4. GIT disorders: GSE (CD) & U. Colitis (rare)
5. Autoimmune ass.: AICTDs.

- Prognosis of LABD: In Majority of cases; resolve after 3-6 yr:

(10-15% in 3rd-6th)

Treatment

- Others:
  1. Cs (systemic)
     - مكلفة تتابع ضغط للدم
     - عشان تتطي بيكب أنفل
     - Usually Needed for pt. & IgA & IgG deposit
  2. others (empirical) (أخرى)
     - Tetracycline, dicloxacillin & Erythromycin
     - other Immunosupp.

- أهم علاجين
  1. Dapsone: (أول) → dramatic in 1-3 d.
     - children: 1 mg/kg/d
     - Adult: 100-150 mg/d.
  2. Sulphapyridine (سلفابيريدين)
     - 1.5 - 3 gm.

سؤال إضافي

	DH	LABD	BP
• HLADQ2	>90%	30%	20% (NL)
• Enteropathy	>90%	Rare	No
• lesions skin	Grouped: papules & vesicles at Extensors	Vesicles or Bullae discrete, grouped or Crown of Jewels. either DH or BP like	discrete Bullae, Trunk & extremities.
• MM	No	• Severe	• uncommon & mild
• HP	Subepid. bullae ē Neut. infilt.	Subepid bullae ē Neut. infilt. & ± Eosinophil	• Subepid bullae ē Eosinophilic infilt.
• DIF	• Granular IgA at Dermal papillae	• Linear IgA & ± IgG at BMZ	• linear IgG & C3 at BMZ
• IIF	• ± Ve	• See before	• See before
• Dapsone Response	Excellent	Good ± Cs	• weak

EBA (Epidermolysis Bullosa Acquisita) (4-1)

- Any age but usually (40-50 y).
- Associate ±:
  - IBD (specially Crohn's) ← "most common"
  - Mg → lymphoma
  - AICTDs

C/P: 2 Types

- Inflammatory Type (Generalized, Non scarring)
  - B.P (Dermolytic P.) or like.
  - CP
    - ↓
    - wide spread tense bullae → No scarring
    - ↓
    - HI (good prog. / responsive)
      1. Cs
      2. Dapsone
      3. Immunosupp
      4. IVIG
- Non-Inflammatory (localized, scarring) — more common
  - DEB or PCT (like)
    - ↓
    - Skin: Traumatic blistering → (↑ Fragility) scar, Hyperpigm. & Milia. (Acral & Trauma sites: elbows, knees, dorsal Hand & feet)
    - Hair → scarring Alopecia.
    - Nail → dystrophy
    - MM → usually affected. (HI) [prolonged / resistant to HI]
      - ① avoid Trauma
      - ② wound margin
      - ③ # ...
  - [So called Acquired Mechanobullous]

HP

↓

Subepid (Sub LD) @± L.L Blistere

- Neutrophil → inflamm. type
- non inflamm. type → Absent or Sparse infilt.

DIF

↓

100% linear IgG & ±C3 at SLD & ±L.L

IIF

↓ (50%)

Anti Collagen VII IgG Antibodies

of EBA

(very chr. dis & very resistant to #)

- No universally accepted # d.t lack of studies & rare cases.

- Best # by some authors:
  - (1st) Steroid + Dapsone or Sulphonamides (ex)
  - (2nd) Colchicine
- Other lines:
  - Pulse Cs
  - AZath.
  - MTX
  - Vit. E & C
  - Ciclosporin
  - IVIG
  - Plasmapheresis

Bullous SLE

- IgG & IgA against Coll 7
- during exacerbat° (WLS)

- Def. Transient autoimmune blistering condition that occurs in the setting of SLE (1% of cases)
- NB: there is some controversy as to whether the term include all bullous erupt° in SLE or should be reserved for those in derma Ag. [Coll 7].
- CIP / Typical Criteria for Ø (see CTDs)
- Histopathology "Lever" 3 Histologic pattern:

Subepid. Blistering in dermal Neut. Microabscesses

1. DH like → Most Common.
2. Basal cell layer vacuolizat° & subsequent blistering
3. vasculitis & subepid blister & pustule format°.

(to diff. from DH: - Mucin deposit (among Collagen)
- Thickening of BMZ.

BSLE

(Photodistributed) ↑ Specially

1. CIP: SLE picture + Generalized blister
2. HP: Subepid blisters ē neutrophilic Infil. ± DH or LABD like
3. DIF & IIF: EBA like.
4. Steriod., Dapsone, MTX or Rituximab.

Self limiting ↓

Ncell So How to diff.

- EBA
  - Trauma site
  - Skin fragility
  - Heal ē scarr.
  - IgG only

- BSLE
  - sun exposed areas (mainly)
  - Hx & manif ☐ SLE
  - dramatic resp. (+) dapsone.
  - IgG & IgA.

Ipaf 2 diseases ē dramatic Response to Dapsone ?? → DH & BSLE (also LAD)

EBA & B.P

عكس اوبان

- Blister → B.P: L-L. / EBA: SLD.
- infiltrate → Eosin. / Ncut.
- C3 → : B.P > IgG (which) EBA only
- Salt split skin Test (SSST)
  - BP: roof side.
  - EBA: dermal side
- Skin Biopsy & Immunohistoch
  - Collagen 7 Abs < BP: at base of blister / EBA: " Roof " "

DIF: EBA → U serrated pattern / BP linear.

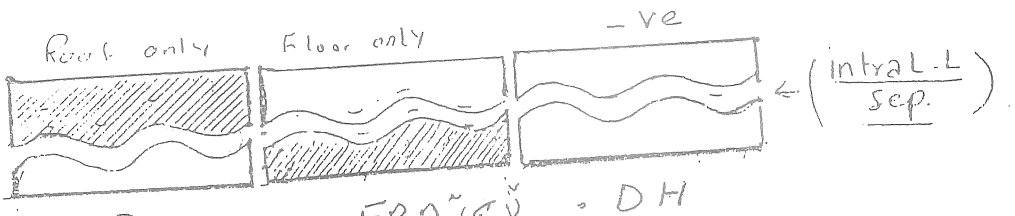
- EBA & BSLE → clinical
- BSLE → clinically as → DH or B.P / Immunologically → EBA.

SSST: "Salt split Skin Test"

Subepid. واهبتا واحد لكل

Separation of DEJ through (L.L) by factor.. exposure to hypertonic 1 molar Nacl for 1-2 days at 4°c, (IS) essential for IF evaluation of subepid bullous dis.

- Can be done for both DIF & IIF., the later the aulo Abs will react the epid. or dermal side of Skin.



- BP
- CP
- HG
- LABD (Majority)

(anti Bp Ag2)

- EBA
- BSLE
- BP (anti-P 105)
- CP (anti laminin CP)
- LABD (minority)

- Dapsone in Subepid. Blistering dis.
  - localized CP
  - DH
  - LABD
  - EBA
  - BSLE
  - SCPD

- Coll 7 Autoimmun bullous → EBA, BSLE, ± LABD
- Coll 7 Non N N : EBD.

Non Auto Immune Bullous diseases

Subcorneal pustular dermatosis (Sneddon & Wilkinson, 1956)

It is a chronic benign/relapsing/pustular eruption which affects mainly the trunk, spares the face and mucous membranes and histologically shows subcorneal bulla which contains polymorphonuclear leukocytes.

- **Age:** 40 - 50 ys., **Sex:** more in female (4:1).
- **Clinically:** Chronic relapsing disorder, with sterile pustules in annular or serpiginous patterns mainly on the abdomen, axillae, and groins. Pus accumulates in the lower half of large pustule (level). Healing occurs with superficial crust and later on with brown pigmentation. **The face is never affected nor the mucous membranes.**
- **Associations:** IgA monoclonal gammopathy, pyoderma gangrenosum, inf. bowel dis.
- **Histopathologically:** Subcorneal neutrophils. Later, few 2ry acantholytic cells are seen at the base of a pustule (probably due to proteolytic enzymes present in the pustular content). Dilated capillaries and perivascular mainly neutrophilic infiltrate are present in the underlying dermis.

  Some authors believe that subcorneal pustular dermatosis is a variant of pustular psoriasis, however, spongiform pustules occur only in pustular psoriasis.
- **Treatment:** Dapsone 50-150 mg daily or sulfapyridine.

Subcorneal or intracorneal separation with:

Neutrophils predominant	Eosinophils predominant	No or few inflammatory cells
• Impetigo contagiosa	• Erythema toxicum neonatorum	• SSS syndrome
• Pustular psoriasis		• Bullous impetigo
• Subcorneal pust. dermatosis		• Pemphigus fol.
• IgA pemphigus (SPD type)		• Pemphigus erythem.
• Candidiasis	• Eosinoph. pust. folliculitis	• Miliaria crystallina

NB:

SCPD like dis

- pustular PS.
- SCPD like IgA Pemphigus.
- Microbial pustulosis of the folds
- Pyoderma Vegetans.

(1939) اكتشف Hailey - Hailey (HH) (Darier اخو ال)

(Familial Benign chronic pemphigus)

Inheritance:
- AD
- + FH → (60%)

Age: 30-40 ys.

Pathophysiology: Genetic + others
- defect on gene called (ATP2C1)
  Chromosom: 3q21-24 → Codes For → Protein hSPCA1
  ∵ is Ca+ & Mn. pump → defective
  desmosomes (depend on Ca+) → separate

Other Factors Share in the dis: (5)
- Heat, Frict, Inf (Bact & Yeast), Sweating.
- UVB: provoke acantholysis (& used to detect Gene Carriers).
- lithium

DD: Darier:
1. Age
2. Gene & protein
3. site: Flexural (Darier: Seborrhic & Flexural)
4. No hand lesion
5. rare MM
6. Nail: white
7. No: Salivary, Ocular, Neuro.

Ultrastructural studies: KCs show:
- retracted tonofilaments
- Elongated memb. microvilli
- ↓ No of desmosomes.

C/P: → Flaccid Vesiculopustules: crusted lesions, circinate, vegetating — 8 HP, 9. HP — to be Stick
- that rupture → Crusted lesions or
- form expanding Circinate plaques ē central healing → pigmental or
- Form moist, Malodorous flat soft Vegetat ē painful Fissures & (2ry Inf.)

Site → Flexures (one site or Multiple sites)

Pain, burning & itching → limit the mobility of Flexures.
Bad odour

other ass. Cut. lesions:
- Pp pits, white nail bands → 4^ → Darrier.
- Mucosal: (rare) oral (oft) ± Vaginal or Esoph.

Darier: Nail: Red & white Bands. MM: Common

- Complications: 1. Kaposi Varicelliform eruption
  2. ACD
  3. Malignant transformation → SCC (نادر)
- prognosis: Exacerbate usually at warm seasons.
  improvement ± occur in old ages.
- pathogy:
  - Dyskeratosis (±) عكس التقرن
  - Acanthlysis: (++)

Darier: Acanthlysis + Dyskeratosis but Dysk. > Acanthlysis.

Suprabasal Acanthlysis: partial or less extensive (+V)
→ Few bridges (desmosomes) remains → Dilapidated brick wall

Villi inside the Blister cavity.
(Elongated dermal Papillae) & a single layer of Basal Cells lines the Villi.

- ultrastructure: → dissolute of Desmosomal plaques → KIF
  Separate → aggregate around Nucleus → Dyskeratosis
- IF: → ??
- Treatment [Course Waxes & Wanes].

1. Topical:
   - Soothing Compresses: Alum. Acetate (1:40) dilute 20% in Alcohol
     Alum. chl.
   - Topical Cs
   - Topical Antib. & Antifungals.
   - Diavonex (Control Ca+).
2. Systemic:
   - Antibiotics (tetracycline & Erythromycin) → ~ Protease Activation
   - Cs (-- Acanthlysis).
   - MTX
   - Retinoids (Few reports +ve Emed.) [عكس التقرن] → [Darier Cure]
   - PUVA (±)
3. Recent
   - Botox → ↓ hyperhidrosis.
4. Grenz Zone Therapy.
5. Surgical: dermabrasion + Co2 laser, Cryo

Genetic Blistering diseases

- Darier
- Hailey-Hailey

Ethiopathogenesis مقدمة لعوزة

- Desmosome كيعمل دور في تركيب ال Ca^{+2}.
- مصدر هذا ال Ca^{+} هو سيتوبلازم الخلية (Cytosol).
- ال Desmosome كيتكون من بروتينات بيتم تكوينها في عضوين من أعضاء الخلية بالترتيب.

1. Endoplasmic Reticulum (ER) Then:
2. Golgi apparatus

ER
G.A ← من السيتوبلازم الى داخل ← تكاثيم ضخ ال Ca^{+}.
تختلف بروتينات هي

ATP2A2 & SERCA2

A. ER ← كتاع لبروتين ← SERCA2 (Sarco or endoplasmic Reticulum ATPase 2 protein)

وهذا البروتين إسمو كتضيفر هو جين أسمه

[ATP2A2] Gene.

ATP2C1 & hSPCA1

B. GA ← كتاع لبروتين ← hSPCA1 (Secretory Pathway Ca^{+}/Mn^{+} ATPase-1) protein

وهذا البروتين إسمو كتضيفر هو جين

[ATP2C1] إسمو

1. Gene: ATP2A2 ← encodes ← hSERCA2 protein → Pumps Ca^{+2} from cytoplasm to ER
2. Gene: ATP2C1 ← encodes ← hSPCA1 protein → Ca^{+} Pumping To Golgi

---

- ت Genetic Mutate in Any of The 2 Genes:

(1) Defective Desmosome → Acantholysis

(2) protein Accomulate inside ER & Golgi → Apoptosis or Dyskeratosis.

Darier Disease

(Keratosis / Dyskeratosis Follicularis)

- **Etiopathogenesis:** AD Genetic + Environmental
  - Mutate in ATP2A2 gene on chromosome 12q24 → defective $SERCA_2$ protein → Failed Ca+ pump in ER → Acanthylosis & Dyskeratosis
  - Environmental:
    - Heat
    - Friction
    - Infection
    - UVB
    - Lithium
    - Premenstrual
- **Epidemiology:**
  - Age, 6-20 y., M = F.
  - Course: Exacerbation (تفاقم) & Remission.

CIP

Skin

(1) dirty, Crusted, Keratotic, red-brown papules at Seborrhoea sites:
- Face
- Marginal scalp [Postauricular] (بعد الأذن)
- Lat. Neck & upper Trunk
- Flexures (DD H-H)

- Coalescence of lesions → Macerated & Papillomatous plaques → Bad odour (رائحة كريهة جدا، تعفن الكتان للوقيا)

(2) Guttate leukoderma: in dark skin individuals.

(3) Hands
- Dorsal: plane wart like lesions; also feet, legs & arms.
- Palmar: Keratotic Pits & papules.

- Systemic manifs: Salivary, ocular & Neuropsychiatric Complications.

MM (15-50٪)

- whitish papules specially at palate.

Nail (الأظافر)

1. longitudinal white, red or alternating white & red lines (Sandwich Nail)
2. Distal V-shapped Nicks / Notches
3. longitudinal ridging, Fissuring & Brittling.

الأعراض المميزة
- Seborrheic
- Flexural
- Hands
- Nails
- MM

Nail
- Leukonychia
- Erythronychia
- V-Nicks

- **Clinical Varieties:**

1. Segmental Darier: along Blashko lines.
2. Acral Hemorrhagic: Hge into acanthelytic Vesicles; red-blue-black macules at palms & Soles also dorsal aspects.
3. Warty Dyskeratoma. (Solitary Darier)

- **Complication of Darier:**

1. Malodour, Pain, itching & burning sensation
2. Kaposi-Varicelliform Eruption: (See Viral)
   [Local infection] - لكمة نيكم KVE حالات
   of disturbed skin barrier
3. Salivary gland obst. → painful swelling
4. Ocular: ulceration & Inf.
5. Neuropsychiatric changes: Epilepsy, mood changes, intellectual Impairment.
6. SCC (cut-& oral)

- **Histopathology:** Acantholytic Dyskeratosis
  = Acantholysis + Dyskeratosis (2 Types of Dyskeratotic Cells).

Suprabasal & Eosinophilic Infilt. (بلاسما) bullous

Corps Ronds
- at lower epid (spinous layer)
- large Cell (KCs)
- Darkly Stained, Partially Fragmented Nucleus surrounded by Clear Cytoplasm & encircled by bright ring of Collapsed Keratin.

Grains
- upper epid. (St. Corneum)
- Small Cell
- Shrunken nucleus
- Intense Eosinophilic Cytoplasm.

DD

A Clinically

(1) Flexural lesions — P. Vegetans, Pemphigoid Vegetans, Pyoderma Vegetans, H-H. (3 Vegetans)

(2) Dorsal Hand lesion (Plane wart like lesions)

(i) Acrokeratosis Verruciformis of Hopf

Forme Fruste (Incomplete Type of Darier)

- AD
- ATP2A2 gene mutation
- dorsal Hand lesions ± Nails
- No — Acantholysis Nor Dyskeratosis.

(ii) EDV

(3) Truncal lesion: Grover (TAD)

B Histopathologically: Acantholytic Dyskeratotic Dermatoses.

(i) Darier
(ii) H-H
(iii) Grover
(IV) Warty Dyskeratoma (Solitary Darier) — واحدية
(V) linear Acantholytic Dyskeratotic epid. Nevi

Treatment

(1) General: • Cotton clothes, sunscreens, ↓ Fric & moisture,
• Antibiotic & Antifungal cleansers (↓ odour)
• Keratolytic & Emollients.

(2) Topical: Cs, 5FU & Retinoids.

(3) Acitretin & Isotretinoin: very effective (Except in predominant bullous or Intertrigenous lesions → Aggravate)

(4) Ciclosporin: if Failed Retinoids.

(5) OCPs: in Premenstrual Flare

(6) Surgical / Laser — Erbium / Co2: To remove The plaques (Vegetating).

Histiocyte

Cell seen all nucleus Image

MCs :

- Ana epid.
- CRP
- Skin Psyp

Nevus :

Rat bite

- Mouse

- NAR : 10 - 20°

Mnemonic

- ID Scalp : Cano ty
  & Thed.

Most Common Cans

- Idiopathic

AV ← AD
PJ

SCalls

Fine — AD, Fungal

Bran like — SD

Shred-like

- Blood Culture

CIP:

Site: The medial Ankle a most frequent & severly involved area (because it represent a water Shed area with relatively poor Blood Flow Compared with rest of the Leg); with advancement of the dis → encircling of ankle, Below Knee Extension (Stocking Erythroderma) & ± dorsal feet.

lesion:
- Reddish-Brown discoloration is the Earliest sign.
- There are Severe acute inflammatory, weeping Patches & plaques that may be ass. with: Honey-colored crusting (d.t bact.) or Monomorphous pustules (d.t cut. Candidiasis).
- long Standing lesions may show:
  1. Hyperpigm.
  2. lichenification ?? (Hemosiderin deposits)
  3. Lipodermatosclerosis (Dermal Fibrosis with inverted Champagne bottle appearance).
  4. Pseudokaposi Sarcoma = Angiodermatitis:
     - unique feature may be seen in stasis D/D by Violaceous Nodules & plaque on dorsal feet that may undergo painful ulcerate Simulating "Kaposi Sarcoma"
- x, Skin may show other Venous insufficiency Changes:
  - Edema
  - varicosities
  - Atrophie blanche
  - Hyperpigm. (d.t Hemosiderosis)

Complications:
1. Impetigonization & 2ry bact. inf.
2. Cellulitis.
3. Id reacts.
4. lichenification.
5. Hyperpigm.
6. lipoderma bSclerosis.
7. Atrophie blanche
8. ulcerate: (Stasis ulcer)
9. CD (specific it)

Investigations:
1. Doppler studies → diagnosis of DVT & Valve incompe).
2. Histopath. → Eczema + Hemosiderosis.

(اللي جاي) NBC diff. bet Pseudokaposi & Kaposi:

- Pseudokaposi: Typical Changes of Stasis D. + Capillary & Fibroblas Prolif. ← Preexisting
- Kaposi: Vascular Slit + Atypical endothelial Cells + prolif. of Vs independant of the preexisting one.

Treatment (اشكر تقل / كيفية جراحة وطبية) (2ary)

Compressing therapy

(1) by specific Stocking that deliver combined Gradient of pressure. (جوراب الساق)

(2) always Leg elevation. رفع الرجل لأعلى من مستوى القلب (lowest leg Edema) لتقليل تورم الرجل وألم الرجل.

Assuring of arterial circulation as if there is impaired Circulation → ↑ Claudication & ± Ischemic damage.

Medical th

1. Acute weeping: Ecz. → Burrow Sc. + Med. ساعد Potent Cs (Oral)
2. Chr. Stasis D. → Calcineurin inhibitors why (No Atrophy & No Tachyphylaxis)
3. th of Inf.: Topical & Systemic Antibiotics

CD لازم Neomycin Bacitracin

Surgical th

1. Incompetent perforators → Ligation
2. Hemosiderosis → IPL (2nd)

Recent th

- Use of drugs that — Neutrophil Mediated cytokines Release as:
  1. Pentoxifylline
  2. PGE1.

4. Systemic Cs. if there is systemic autoEczematization
5. long Term: Emollient ✓ under occlusion..

لاحظ: شرط استعمال الـ Cs

1. oint.
2. Med. Potency (Low potent → Systemic abs. Atrophy / ulcer)
3. Not for long duration

Acroangiodermatitis

(**Synonyms:** pseudo-Kaposi's sarcoma, acroangiodermatitis of Mali-Kuiper, gravitational purpura, stasis purpura)

- **Definition**: was first coined by Mali in 1965. [1] It is a proliferation of *pre-existing vasculature* seen in venous hypertension, arteriovenous malformation, or acquired iatrogenic arteriovenous (AV) fistula.
- Etiopath. : Chr. Venous insuff. → Venous HTN → Tissue Hypoxia → Neovascularization / Fibroblast prolif.
- **C/P:** Confluent, violaceous or brown-black papules cover large areas of the distal parts of the legs. Ulceration and bleeding are sometimes noted. Bilateral lesions are usually associated with chronic venous insufficiency, whereas unilateral lesions suggest an underlying vascular malformation.

- Types :

[1] Mali Type → ass. with Stasis Dermatitis

[2] Stewart-Bluefarb Type → ass. with Cong AV malformat.
e.g. Klippel Trenaunay synd

[3] Dermite OCre of Favre : ass. with Pregnancy.

[4] other Types :
(1) AV Fistula of → shunt in CRF, stump Dermatosis in Amputees.
(2) HCV ass. (EMed. 2010).

	Acroangiodermatitis of Mali	Kaposi's sarcoma
• Hp	Small dilated vessels lined by plump endothelial cells with hyperplasia of pre-existing vasculature	Slit-like spaces and spindle cell proliferation. Vascular proliferation is independent of the existing vessels
• PAS	+ ve	- ve
• Factor VIII (B) Ag in Endoth.	+ ve	- ve
• CD34	Positivity seen on endothelial cells of hyperplastic vessels	Positivity seen on both endothelial cells and the characteristic spindle-shaped perivascular cells
• RBCs extrav. Hemosiderin (Fib)	Present	Present

Treatment

1- Correction of the underlying chronic venous insufficiency and vascular malformations

2- ***Systemic therapy:*** Various medical modalities of therapy have been tried with favorable results but options are limited. Oral erythromycin 500 mg four times a day
Dapsone

3- Topical CS

4- Vascular lasers.

Dyshidrotic Eczema
(Pompholyx, Vesiculobullous hand eczema)

Def: Dyshidrotic eczema is a recurrent or chronic relapsing form of vesicular palmoplantar dermatitis of unknown etiology. Dyshidrotic eczema also is termed pompholyx, which derives from *cheiropompholyx*, which means "hand and bubble" in Greek.

Etiology and pathophysiology: The etiology of dyshidrotic eczema is unresolved and is believed to be multifactorial. Dyshidrotic eczema is considered a reaction pattern caused by various endogenous conditions and exogenous factors: ☺ ± :

* 1. Genetic: → AD Familial pattern ± present
  ↘ Pomphdyx gene in Chromosome 1@q21.1-3
2. Atopy (50% of cases).
3. dyshidrosis: . Not a cause but associate it in 40% of cases & its tt improves Pomphdyx.
4. Emotional Stress.
5. CD (Nickel or Cobalt in diet).
6. Septic foCus eg Strept or dermatophytide.
* 7. Drugs: . Aspirin, IVIG & PUVA.

. CIP : Acute onset of erupts of Bilat & Symmetrical Deep seated vesicles & Bullae at Palms (Cheiropomphdyx), Soles (Pedopompholyx) or Both. Nail fold may be affected → Nail dystrophy. ass. ē severe itching & Burning.
. ExaCerbat⁻ & Remission is Common (& Chronic Vesiculo-Bullous Eczema)
. unilat. Cases may be d/t CD.
. 3rd Most Common type of Hand EZ., usally affect middle aged.

. tt 1. Treat the underlying cause.
2. Vesicular lesion → drying Antiseptics
3. Chronic ✓ → Cs, Emollients & Keratolytic
4. Resistant Cases: . Systemic Cs
. MTX
. Radiation

. DD : pustular Psoriasis of palms & soles

Ref.
All Sources

Asteatotic Eczema
Eczema craquelé, Xerotic eczema, Chapping

Def. Eczema Characterized by pruritic, dry, cracked, and polygonally fissured skin with irregular scaling . It most commonly occurs on the shins of elderly patients, but it may occur on the hands and the trunk.

Etiology and pathophysiology:

Causes

***Multiple etiologic factors may coexist to cause asteatotic dermatitis, including the following:** *(All are associated with ↓↓lipid content of skin):*
(or water)

- **Aging:** due to ↓↓sebaceous and sweat glands activity and ↓↓ Keratin synthesis.
- **↓↓ humidity and cold:**→ increase the loss of water by convection.
- **Wrong Behaviour** :-Frequent or prolonged bathing in hot water and use of soaps, infrequent use of emollients and use of Degreasing agents (Solvents and Cleansers)
- **Atopy**
- **Ichthyosis**
- **Radiation**
- **Drugs** - Antiandrogen therapy[5] and diuretic therapy
- **malabsorption and Nutritional deficiencies** of essential fatty acids, including linoleic acid and linolenic acid , Zinc deficiency[3]
- **Thyroid disease** - Myxedema and other thyroid diseases with diminished sweat and sebaceous gland activity[4]
- **Neurologic disorders** - Decreased sweating in denervated areas
- **Malignancies** - Malignant lymphoma,[6] gastric adenocarcinoma,[7] glucagonoma, angioimmunoblastic lymphadenopathy,[8] breast cancer, large-cell lung carcinoma, and colorectal carcinoma[9]

Epidemiology: *Age:elderly>60 y. *Sex:M>F

c/p: Primary lesions: Slightly scaly, inflamed, curvilinearly cracked and/or fissured skin most commonly involves the pretibial areas, but it may also occur on the thighs, on the hands, and on the trunk *(Fitzpatrick likened asteatotic eczema to a dried-up riverbed).*

- Secondary lesions :Excoriated, erythematous, edematous patches may result from rubbing or scratching.

Clinical types: 1-localized: usually pretibial.
2-Generalized (Ichthyosis): 2 Mg

III

تدابير للمريض : الجام جاف لازم :

1. لفترة كبيرة (٥-١٠ دقايق)
2. بماء دافئ
3. بدون صابون
4. بدون صوف
5. استخدم Humidifier

1

2

Emollients:

(for AD) استخدامه بعد الحمام مباشرة.
استخدامه دوما : عدد مرات الاستحمام.

3 Topical Cs:

- Mild Topical Cs (III-VI)
- تبدأ باستخدام طريقة
- عدد المرات

2
(A) Soaking & Greasing (B) Under occlusion for 1-2 hs

- Soaking and Greasing:
(Soak & Smear) Technique:
- Soaking: of affected part in Tepid water for 15 min.
- Greasing (Smear): Immediate use of mild Cs oil.

Nummular Eczema

(Discoid Ecz.)

Def. Type of Endogenous Ecz. **ch BY:**
well defined, Coin-shapped, scaly, plaques usually on arms & legs, w are very itchy & very persistent

- **AET & pathophysiology:**

"Atopy" (1.) AD (recently considered as Adult onset AD)

(2.) Infect. (staph usually colonize or infect it).

(3) Emotional stress.

(4) Xerosis

Clp. Discoid plaques ch BY:

- May undergo central clearing → Annular lesion.
- Very itchy, very chronic
- usually at: Forearms, legs, Hands, Lumbs & Trunk
- Staph. has a Marked Role.
- More in Elderly (60-70s).

Is there a cure for nummular dermatitis?
No. However, the disease can be controlled. Many of the same principles apply here that apply to the treatment of atopic dermatitis. Limiting baths and soap exposure, avoiding irritants, frequent use of emollients, topical corticosteroids, avoiding dry environments, and antihistamines all have a role in treatment. Topical corticosteroids are the mainstay of therapy. With the high rate of staphylococcal colonization, many dermatologists routinely prescribe a 2-week course of oral antibiotics, such as dicloxacillin or cephalexin. Systemic steroids should be used only for severe cases and limited to a tapered course over 2–3 weeks. Severe chronic cases may also benefit from PUVA.

Does nummular dermatitis resolve spontaneously?
Yes, but not often. In a prospective study of patients followed for 2 years, 22% were disease-free. Another 25% were free of lesions for weeks to months, but 53% were free of lesions only with continued local therapy. If there is no clearing within 1 year, the disease tends to persist for many years.

(Emal 2009)

Pityriasis Alba

def: Non specific dermatitis of unknown Aetiology That causes Erythematous scaly patches → These resolve & leave areas of Hypopigm. that slowly repigment to NL.

Aetiology: unknown but ± d.t:

1. Atopy
2. Strept. inf.
3. Sun Exposure (ضد)
4. ↓ Zinc.
5. ↓ Fe
6. Parasitic infestations.

7. Malassezia: produces a substance called pityrictrin → sun filtrat: (prevent natural sun Tanning)

Clf: (1) usually affects dark skin children at summer

(2) has 2 stages:

- Early: ill defined pink erythematous, scaly lesion →
- Late: Hypopigmental (ill defined & scaly)

(3) usually a/r sun exposed areas

(4) Clinical Variables:

(i) Classical Type: a/r Sun-exposed areas.
(ii) Generalized ": Bilat & Symm.
(iii) pigmenting ": Central brown Pigmentation surrounded by ill defined slightly scaly Halo at the face.

Treatment: (1) Treating the cause e.g. Sunscreen, Parasites, Vit. deficiency...

(2) Early stage → Hydrocortisone 1%
Late " → Emollient

(3) Some Authors: Local Calcineurin Inhibitors (Similar to Tacrolimus 0.1% ointment)

Juvenile plantar Dermatosis

(DNNZ)
. Andrus
. Resk (19)

def: Eczema affecting the feet of Children.

Aet: . Repeated Friction & Macerat of feet by: "الاحتكاك"

1. occlusive shoes specially Athletic Shoes
2. Abrasive effect of pool surfaces or diving board
3. (Thin) non-absorbant Synthetic Socks.

4 Some consider it manif. of AD.

• يعتقد ان سببها هو التغير الى الجلد في آخر ٢٠ سنة في صناعة الاحذية وشرابات الاطفال حيث تم استبدال مواد الطبيعية (صوف - قطن - جلد) بمواد صناعية (نايلون - بولستر) والتي تمتاز بانها repellent لكل الرطوبة بالاضافة الى تنظيف الاحذية بمواد كيميائية مما يؤثر على durability وعلى كفاءة الجلد.

All these: ↑ Humidity → Feel macerat → sweat retent → aggravate the condition

(So role of Friction considered) ← يعتبر سبب رئيسي لاصابة الاطفال بالتهاب الجلد ولكن ليس السبب الوحيد

• CIP: 1. Age: 3 Ys – puberty (14)

2. Start as bilat, symmetrical red glazed smooth patches at medial or dorsal aspect of Big Toe → then spread to involve weight bearing areas of feet as forefoot. (Heel less affected).

Note: Webs & arches are spared.

DD: . AD : Psoriasis
. CD . Fungal inf.

Treatment: (1) Reduce friction: تقليل الاحتكاك (مكن كفء لاحذية عند الطفل) وتغيير شرابات وتغيير الحذاء (proper Foot Wear).

(2) Emollient.

(3) Have rest day: schedule quite time & little or no walking to allow for Healing of fissure

(4) Topical Cs.

Hand eczema

Hand eczema is such a common and distressing condition, and poses such difficult problems for the dermatologist, that it deserves separate consideration . Up to 30% of occupational medical practice relates to hand eczema, with important issues regarding medical litigation, worker's compensation and disability. One-quarter of the patients referred to a specialized contact dermatitis clinic suffered from hand dermatitis.

Classification: 1-Etiologic classification 2-Morphologic classification
(Rook) 3- Classification Acc. to the Age.

1-Etiologic classification

Exogenous	*Endogenous*
1-ACD: -Delayed hypersensitivity (type IV) (e.g. chromium, rubber) -Immediate hypersensitivity (type I) (e.g. seafood) 2- ICD: -Chemical *(e.g. soap, detergents, solvents)* -Physical *(e.g. friction, minor trauma, cold dry air)* 3-Ingested allergens *(e.g. drugs, possibly nickel, chromium)* 4-Infection *(e.g. following bacterial infection of hand wounds)* 5-Secondary dissemination *(e.g. dermatophytide reaction to tinea pedis)*	1- Atopic 2. Dyshidiotic (Pompholyx) 3. Psychosomatic (??. Eczema > Initiation) 4. Idiopathic (Discoid & Hyperkeratotic palmar Ecz.).

2-Morphologic classification

1-vesiculobullous hand eczema(Pompholyx) / &Patchy vesiculosq.
2-hyperkeratotic hand eczema (Xerotic Ecz.)
3-dry palmer eczema (House wife Ecz)
4-finger tip eczema
5-ring eczema (6. localized thumb Ecz.)
7-discoid eczema
8-chronic acral dermatitis (Hand Ecz. + ↑ IgE)
9-apron eczema
10-gut eczema
11-other patterns (eg.patchy vesiculosquamous)

[1] ... - ... ...

• Treatment [2] Potent or Superpotent Cs For 2-3 wks → Week-end

[3] ±5 ds / wk → Weak Potent Cs + Tavolimus...

[4] Emollients: ...

Lichenification

Introduction

Lichenification is a pattern of skin response to repeated scratching or rubbing, characterized *histologically* by acanthosis, hyperkeratosis, and elongated rete ridges, and *clinically* by a thickened skin, with accentuation of the surface makings so that the affected skin surface resembles *tree bark*. It may be primary (lichen simplex), without an itchy skin disease and caused by emotional tension, or secondary to an itchy skin disease as venous eczema, atopic dermatitis, chronic contact dermatitis, or chronic infection with T. rubrum of thighs or feet.

Lichen simplex chronicus (LSC)
(localized Neurodermatitis)

Def. Reactive pattern of skin that arises 2ry to repeated scratching or rubbing [so this not a 1ry process] & ch. By cut. lichenification Δ of:
- Thickening
- Hyperpigm.
- Accentuated skin Markings.

- Etiopathogenesis unknown but ↑:
  - Emotional stress → Sensation of (Burning or Pruritus) → rubbing → lichenification → More rubbing → More lichenific.
  (Vicious Circle of itch/scratch cycle)

- Epidemiology: . Age: any but usually 30-50y..
  . Sex: ♀ > ♂

- Clp (1.) itching: . Severe & occurs in Paroxysms of great intensity → true scratching.
  . There is (refractory period) of some hours before until itching recur.

(2.) Skin lesion: . at first: Erythematous, Edematous Excoriated Plaques → chronic picture of lichenification
. Lichenified papules ± seen.

• Site : Most Common sites are:

- occiput
- Nape Neck → Nuchal area (Lichen Nuchae)] ♀
- Perineum & Scrotum (♂)
- wrist & ankle
- Extensor Forearm.

NB : (i) Giant lichenification of Pautrier
LSC in areas of loose CT as Genito-Crural area → Solid Tm like plaque & Warty Cribriform surface.

(ii) Notalgia Paresthetica LSC at Rt. tip of Scapula.

Pathology → see lichenification

DD ① lichen amyloidosis ② L.P ③ Ps.

treatment:

1. Stop itching (Break the itch/scratch cycle):
   - Anxiolytic
   - [illegible]
2. Cs: Topical & ILs
3. Emollient (2009) ↓ (JAAD 2001) ↓
4. Antihistamines, Botox, Topical Aspirin/diclofenac
5. TENS (Transcut Electric N. Stim).

---

other Types of Eczema

- Frictional lichenoid Dermatitis
- Eye-lid Ecz.
- Breast Ecz.

• Sandbox or Frictional lichenoid Dermatitis

- pin-head sized, white papules at friction sites (Elbows, Knees, Bucky, Fingers)
- Etiopath. ?? Friction or Sun.
- DD: lichen-nitidus.

(NB) in Adults: Dermatitis Papulosa Juvenilis

2. Eye-lid Ecz. →

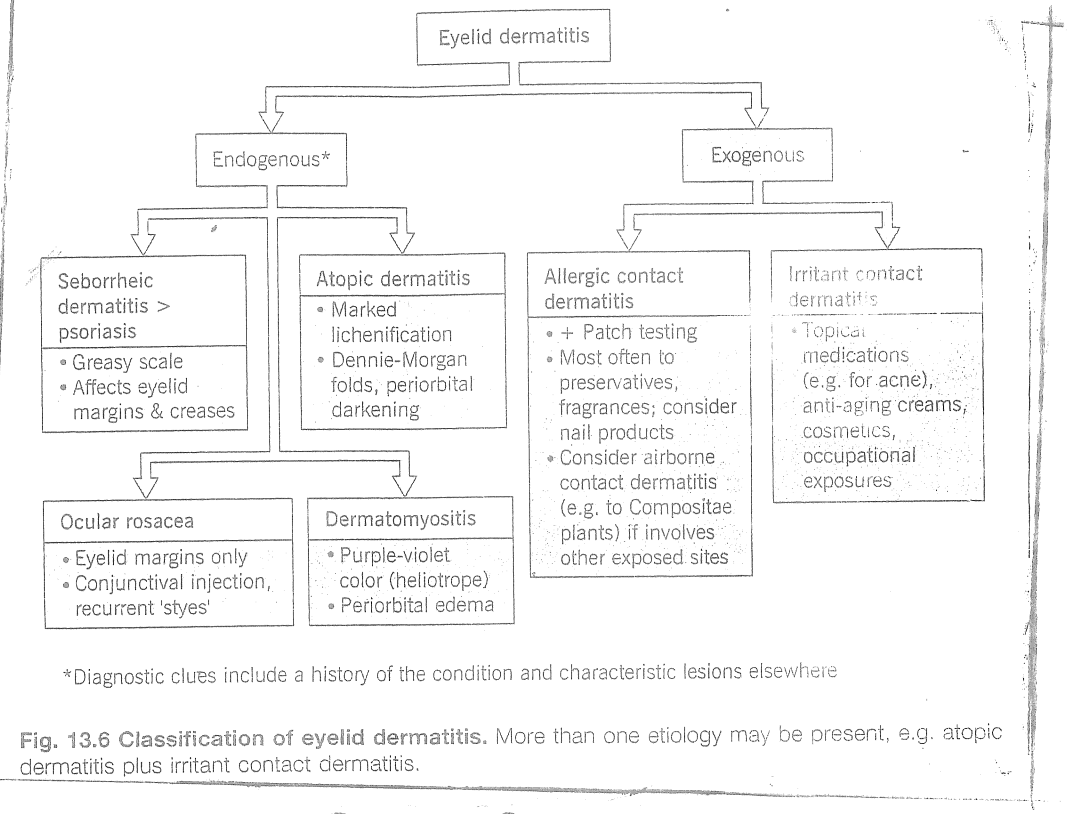


Fig. 13.6 Classification of eyelid dermatitis. More than one etiology may be present, e.g. atopic dermatitis plus irritant contact dermatitis.

3. Breast Eczema (Nipple Ecz.)

- ± Affect. Nipple, Areola & Surrounding Skin. (Especially of Nursing Mother).
- Etiology: CD, ND, AD, SD
- Hx: As Ecz. → if No response → (Biopsy to Exclude "Mammary Paget"):
  - Unilat.
  - Not responding to Cs.

Topical Corticosteroids

Mechanism

1. Antinflammatory
2. Antiproliferative: ↓ DNA synthesis specifically → Lymphocytes & Fibroblasts
   → ↓↓ Collagen → Atrophy
   [all Cs Have These effect except → Hydrocortisone & Dermatology]
3. Immunosuppressive: → CMI: ↓ IL 2,3,4 5,6 → ↓ T cell prolif.
   · ↓ IFN-γ
   HI: ↓↓ Igs production.
4. Vasoconstriction: ↓ → Erythema, Edema, Heat [& Ht of Hemangioma]

[5. Glucocorticoid Activity
6. Mineralo Corticoid Activity

NB → Antinflammatory effect is d.t binding to 2 Types of Rs

- CM Rs
  ↓
  CM disrupt
  ↓
  -- phagocytosis & lysosomal release.

- Cytoplasmic Rs

[A] · Cs + Cytosol → enter the nucleus
→ interact ē Nuclear DNA → product of steroid induced proteins (Lipocortins)
↓
-- Phospholipase A2
↓
-- Arachidonic acid Formation
↓
↓ synth of → PGs, leukotrienes, PAF.

[B] -- COX enzyme.

• Classification According To Potency

I. European: ٤ درجات وهي كالآتي

II. American (الأمريكية): ٧ درجات → Classes

I Superpo
II Potent
III Potent
IV midstren
V midstren
VI mild Po
VII least Potent

(احفظ الأسماء)

• European classification

(احفظ جيداً عشان الفوائم الجاية وشغل السنة)

1. **Mild Potent** (Antinflammatory activity; 1-10)
   - Hydrocortisone (Micort)® (Hydrocortisone)®
   - Aclomethasone (Perderm)®

2. **Moderate Potent** (Antinflammatory : 10-100)
   - Clobetasone butyrate (Eumovate)®
   - Hydrocortisone in urea 1%

3. **Potent** (Activity 100-500)
   - Betamethasone → Valerate 0.1% (Betaderm)®
     → dipropionate 0.05% (Diprosone)®
   - Mometasone (Elocon)®
   - Fluticasone (Cutivate)®
   - Prednicarbate (Dermatop)®
   - Triamcinolone (Kenacort)®

4. **Superpotent** (> 1500)
   - Clobetasol propionate 0.05% (Dermovate)®
   - Diflucortralone Valerate (Nerisone forte)®

Side effects of Topical Cs

- Epidermal Atrophy
- Dermal Atrophy
- steroid addiction synd
- Skin irritability & Fragility
- Striae
- Purpura
- Telangiectasia (rebound VD)
- Hypo-pigmentat^.
- Hypertrichosis
- Perioral dermatitis
- periorbital → Cataract Glaucoma
- Acne vulgaris
- Acne Rosacea
- Exacerbat^ of Skin inf. (Ingonito ↑s glu gra ulc)
- " " Psoriasis
- Delayed wound healing.

---

dg: ↓ Cs effect e prolonged use
- may occur ē in 2w of ##
- To avoid → Systemic absorpt^ → Tincid.ē / Commonest HPA suppr. (1 tube Super Potent ((7.5gm/d))
  - Tachyphylaxis
  - occlusion Complicat^
  - Contact Dermatitis.

1. Super Potent Cs
2. children & infant ??
3. occlusion
4. Wide spread use >50gm/w Super or >100gm/w Pot
5. Region e.g delicate skin & Flexures.

Shift to low potent. | use on holidays | alternative IH eg Diavonex, TCI

• Discussion of Complicats:

Types: ICD / ACD

Cs induced Atrophy & effect on Skin Layers.

effect on epid.
- epid. thining occurs
- After: 1w of Superpotent / 3ws of Potent
- ↓
- thining of Sp. St. Corneum
- ↓
1. impair barrier funct^
2. ↑ TEWL
3. ↑ irritancy & Fragility.

effect on dermis
- ↓ Dermal vol. after 1-3 ws of Superpotent
- d.t (1) ↓ hyaluronic acid synth. by Fibroblasts
  (2) ↑ Water loss
  (3) ↓ Collagen synth. & ↓ elastin., ↓ fibrobl/ast
- ↓
1. dermal Atrophy
2. Striae
3. Telangiectasia
4. Fragility
5. Purpura (d.t poor vascular support)
6. ↓ wound healing

ICD
1. Frequent
2. ± d.t Propylen glycol
3. More ē Cream base [اقل تركيز ممكن]

ACD
- less frequent
- ± Caused by: Cs itself / vehicle / preservatives / Fragrances

How to suspect:
1. Lack of efficacy
2. Worsening of Lesions

- patch test help Sort out this problem.
- ACD more ē Hydrocortisone & Tixocortol & Less ē
  - Clobetasol
  - Mometasone
  - Betamethasone

NB → Skin atrophy may be Reversible ∴ stop:

. Steroid Addiction Synd:

Mid-high or even low potent] Cs applied to < Face / Genitals For several Ws → when discontinuing it → Sensat° of < Burning / Severe itching (symptoms of dermatitis that was treated by it in profound manner)

AEt thining of < St. Corneum / Epid → make the patient more susceptable to irritants

Hg → discontinue Cs or gradual withdrawal & use of emollients & instruct the pt that symptoms may remain for ws - ms till complete cure.

As
- Moisturizers
- Soaps
- Sun screen
- Make ups.

• occlusion complications:

1. ↑ incid of systemic Abs.
2. bad odour
3. Miliaria
4. Folliculitis & infect°
5. Reversible atrophy of adjacent skin.

. Indications of Topical Cs

1. dermatitis
2. pLE
3. DLE
4. AA
5. lichen striatus
6. localized pemphigoid
7. كلنزيرا

. Contraindications

1. Skin manifs. of vaccinat°
2. Cut. TB & S
3. Skin infect°
4. Perioral dermatitis
5. Hypersensitivity.

6. Cut. dis not Responsive or Worsened by Cs:

. all C.Is + Pit. Rosea, PRP, EM, Urticaria

. Dry skin & Ichthyosis, Large Vs vasculitis, parapsoriasis

. Guidlines For use of Topical Cs

1. Acc. to Potency
2. Acc. To Applicat°
3. Acc. To the vehicle.
4. " " Amount

1. Super potent: ± used on Trunk & extremities
   - on small area < 10% BSA
   - not > 2 wks
   - not > 50 gm/w
   - No under occlusion.
2. potent
   - not > 20% BSA
   - NOT > 3 - 4 wks
   - NOT > 100 gm/w

   NB: ± used on FaCe For Period < 2 wks; ± used in children if failed lower Concs.
3. Mod potent → Tried on hand ecz. & Atopy
4. Mild → used for chr. use in: Face, Flexures, infants & children < 1Y.

2. Acc. to applicat

. Method → ↑ per cut. Abs. by occlusion.

. Frequency → used in alternate day therapy

. Type of Cs (Tachyphylaxis, ESS): when using super potent: use it 2/day For 2 wks then Rest For 1 w & Repeat For 2 cycles then → either

(1) Shift to lower potency
(2) use on holidays
(3) alternate therapy eg TCI

3. Vehicle:

1. Oint → Chr. dry lichenified lesion
2. Cream → Acute weeping dermatitis
3. Cream, gel, Alcoholic lot → hairy areas.

تختلف حسب القوة

- Oint
- Emollients
- gels
- Cream
- lotion
- Sol.

4. Amount of Cs used:

1. determined by Finger tip Unit (FTU) which is the amount of Cream expressed from a tube of 5mm diameter from the tip of index to the 1st distal joint. on palmer aspect.

2. 1 FTU = 0.5 gm of medicine = will sufficient To treat 2 palm sizes in the average adult.

Site	FTUs
. Groin or hand	1
. Face or Foot	2
. one arm	3
. one leg	6
. Trunk (front & back)	14

Hidradenitis

(يضاف عليها في شابتر البكتريا)

I-Hurely staging

Table 1. Hurley Classification of Hidradenitis Suppurativa

Hurley stage	Suppurative/fistulous lesion
1	Solitary or multiple isolated abscesses without scarring or formation of sinus tracts or fistulas
2	Solitary or multiple widely separated lesions with formation of sinus tracts or fistulas
3	Diffuse or broad involvement of abscesses across a regional area with multiple interconnected sinus tract or fistulas

II- Treatment according to the stage

Hurley stage	Topical treatment	Systemic	Surgery
Hurley stage I/first-line therapy	Clindamycin Intralesional triamcinolone Resorcinol	Antibiotic Hormonal therapy	Localized surgery
Hurley stage II/second-line therapy		Antibiotic: tetracyclines or clindamycin plus rifampicin	Cold steel excisions CO_2 laser evaporation
Hurley stage III/third-line therapy		Systemic immunosuppressant: dapsone cyclosporine TNF-α inhibitor	Wide excision CO_2 laser evaporation

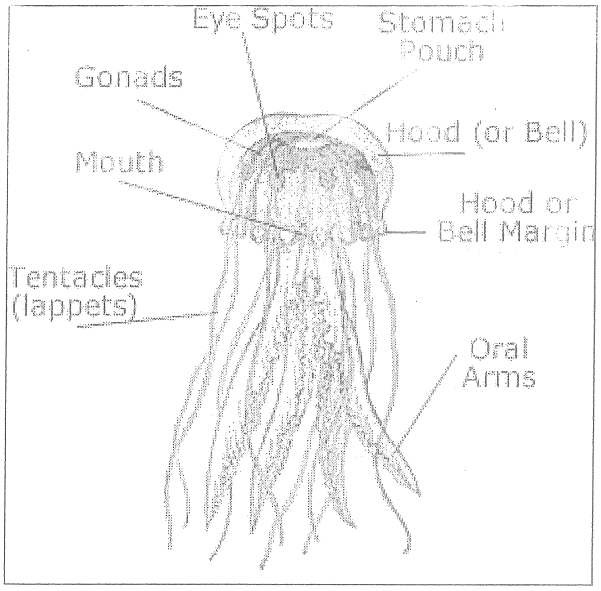
Medscape

Source: Expert Rev Dermatol © 2010 Expert Reviews Ltd

Jellyfish stings

(يضاف علي ورق Eczema..)

Structurally jellyfish comprise a bell-shaped body with tentacles, some up to 30 metres in length. The nematocysts reside within theses tentacles (مخالب). Stings are delivered when contact is made with the tentacles and nematocysts discharge into the skin.



- Jellyfish are most prevalent in calm warm seawater, sandy beaches and harbours during the summer months. However, they are also seen in other circumstances.

Clinical presentation : The first symptom is of pain, often so severe as to lead to loss of consciousness. Some victims of the some types of jellyfish are unable to make it to the beach alive. Other symptoms include:

- Paraesthesia and itching
- Linear & bizarre shapped Red plaques, patches, & blisters that may become nectotic and eschared.
- Swelling, Sweating in affected area
- Nausea and vomiting
- Muscle pain and cramps.

- Depending on the amount of stinging and the type of jellyfish encountered, shock and cardiac arrest can follow.

-After recovering from the initial sting, the wound may later blister and become necrotic (tissue death).

Treatment:

- Avoid moving the affected limb. Do not rub with a towel or use fresh water as this may cause further damage by causing further nematocyst discharge. Contrary to popular belief urine and alcohol can exacerbate injury and are not recommended.

- Remove nematocysts and tentacles from the skin using gloves and forceps. Razor blades can be used to shave off nematocysts.
- If stung by box jellyfish apply liberal amounts of home vinegar (5% acetic acid (5% acetic acid) will inactivate any undischarged stingers and lessen the severity of the symptoms.), or in its absence, salt water or hot water (40C) for 30 minutes. Seek immediate medical attention.
- If stung by the Portuguese man of war, thoroughly rinse exposed areas with seawater (vinegar is not helpful).
- Ice or an ice pack can help with pain while seeking medical attention.
- Antivenin injections are available in some medical centres for specific jellyfish, and are particularly recommended for box jellyfish stings.
- Topical corticosteroid & antihistamines

Zika virus

- Zika virus is RNA virus of family Flaviviridae that is transmitted by mosquitoe & tick bites in tropical areas and has a prominent cutaneous manifestations.- Zika virus it was first described in humans in the 1960s in Nigeria . cases have bee reported in upper Egypt and transmitted by Aedes Aegypti mosquito. - Only about one in 5 people carrying the virus actually develop symptoms from zika virus infection.

Mode of infection:(-IP: 10 days)

- Mosquito bites: Aedes aegypti mosquitoes breed in and around ponds of stagnant water where humans live and usually bite during daylight hours. When a human is infected the virus circulates the blood for 10 days before symptoms occur. It is during this time that the Aedes mosquito may acquire the virus, then bite and infect another unsuspecting victim.
- Sexually transmitted
- MTC: Through Infected birth canal

-Predisposing factors:

- Overcrowding and poor sanitation
- Poor vector control, e.g., stagnant pools of water for mosquito breeding.
- Travelling to endemic areas

- Clinical features:

- FAHM, fatigue,muscle pain, abdominal pain & vomiting
- Conjunctivitis
- Skin Rash: maculopapular (morbilliform) or scarlatiniform. It starts on the face on the first day of illness and spreads all over the body. It begins to fade within 2–3 days and is gone completely within a week.
- Oral MM: petechiae at mouth and palate.

- Complications

- Guillain-Barré syndrome

- Birth defects: The zika virus replicates and persists for several months in the placenta and in the brain tissue of a fetus→GR, fetal loss, microcephaly, brain calcifications &damage

-Diagnosis:

1- Clinical: S&S after Mosquito bites in endemic areas
2- Serology (IgG&IgM): to be repeated after 3 ws if negative

Treatment: The best way to prevent zika virus infections is by preventing spread of the virus by vector control. This means eliminating or controlling mosquito breeding sites. The zika virus-carrying mosquito likes to breed in artificial containers and receptacles containing water in and near buildings.No specific TTT nor vaccine.

Afamelnotide (Melanotan-I)(Scenesse®)

(جديد ..ممكن دكتوراة)

Introduction: α -MSH, production,function & Receptors

1- Pituitary: α -MSH→ ++MC1Rs (Melanocortins Receptors1)→ ↑Eumelanin& ↓ Pheomelanin→ ↓ ↓ UVB penetration→ Photoprotection → ↓ ↓ incidence of melanoma (Afamelnotide , Melanotan-I)

2-Brain: α -MSH→++MC4&5Rs→Regulation of apetite&sexual function (Bremelanotide ,Melanotan-II)

- **Mechanism of Afamelnotide :** α-MSH analogue,acts non selectively on MC1Rs expressed on melanocytes. It ↑↑ production of eumelanin & ↓↓ Pheomelanin thus provides direct photoprotective& antioxidant effects against harmful UVB radiation.

-**Indications**: Photoprotection for 5 diseases:

- Erythropoietic protoporphyria
- Polymorphous light eruption
- Phototoxicity associated with systemic photodynamic therapy
- Solar urticaria
- Skin cancer: AK&SCC.

- Dosage & Administration

- Afamelanotide (Scenesse®) comes as a white rod approximately 1.7 cm in length and 1.5 mm in diameter.

- It contains 16 mg of afamelanotide and is administered as a subcutaneous implant specially around the hip.

- It is inserted every 2 months, prior to and during summer with a maximum of 4 per year.

- Adverse effects:(Few)

- 30% of patients experience hyperpigmentation at the implant site & darkening of moles anywhere on the body

- Mild tiredness, headache, dizziness and nausea after administration of the implant (usually clears by 72 hours).

- Contraindications (Because no available Data)

- Hepatic and renal impairment,
- Ages before17 and after70 and
- Pregnancy (Women of childbearing potential should use effective contraception during treatment with afamelanotide, and for a period of three months after).

Probiotics and Atopic Dermatitis

(Front Microbiol. 2016)

Briefly, hygiene hypothesis inversely relates the prevalence of allergic diseases and urban lifestyles, high standard sanitary conditions, vaccinations, antibiotic administration, and small family size.

- Probiotics are ingested live microorganisms that, when administered in sufficient amounts, confer health benefits on the host. robiotics contribute to regulating allergic hypersensitivity reactions by suppressing the Th2 mediated response that helps in balancing Th1/ Th2 immune responses and by increasing Treg mediated immune responses

- *Lactobacillus,* Bifidobacteria, and yeasts are *the most frequently studied probiotic strain.*

- probiotic milk administration was done 2–4 weeks prenatally to the pregnant mothers and postnatally to the infants for a 1-year time period

- the prebiotic is a specialized plant fiber that beneficially nourishes the good bacteria already in the large bowel or colon. While probiotics introduce good bacteria into the gut, prebiotics act as a fertilizer for the good bacteria that's already there.

- Probiotics for the prevention or intervention of AD is a vast underestimated area of research; and as a result, there is no reliable evidence to date that strongly supports their safe application. In spite of the weak evidence, a considerable number of clinicians prescribe the use of probiotics for the prevention of eczema. The regular instillation of probiotics in daily use at an early age could help in preventing the initiation of eczema. However, several variables, such as the use of antibiotics, prenatal and postnatal diet, mode of delivery, and surrounding allergenic environment in the home, could impact the early-life colonization of probiotic strains. Nevertheless, the clinical administration of probiotics may become more widespread if the remaining questions are answered with strong evidence: what type of probiotic strain should be used? What dosage and time of administration should be used? At what time of life is the use of probiotics more efficacious? And most importantly, should the use of probiotics be personalized? Current analysis of the role of probiotics in the prevention of AD reveals that a positive effect may be related to the type of probiotic strain used, the method of administration, onset time, as well as the dose size and duration of treatment. However, these uncertainties need to be further clarified before corroborating the preventive impact of probiotics in the prevention and/ or treatment of AD.

Pigmentary disorders

Basics

- Color of Skin: caused by 4 Factors:
  1. Hb — oxyHb → red color / deoxyHb → Blue
  2. Melanin → Brown
  3. Carotenoids: obtained from plant diet — orange Carrots.

Melanocytes

- Dendritic, Pigment synthesizing Cells that derived from ! Neural Crest & rests bet. KCs at BMZ.
- Embryology: Melanoblast (at Neural Crest) —differed to→ Melanocytes
  → Migrate to:
  - Skin: Epid., dermis & H. Follicles.
  - Inner ear
  - Eye
  - Meninges
- Important Numbers:
  - development at 8 ws IU.
  - Earliest Signs of Melanization: 10 ws IU
  - No: 2×10^9 (الكبد — Face, Genitalia)
  - No ↓ by 8% / 10 y.
  - MCs : KCs ratio = 1 : 9 (1:4 – 1:10)
  - Each MC supplies Melanosomes to 36 KCs by process of Apocopation (Apical part of ! Cell is released Together with the Secretory product) [Cytophagocytosis]

(1:9) & (36 KCs)

- MC Exam.: by H & E Stain: They appear as a Clear Cells at basal Cell layer & deeply Stained Nucleus ---

(d.t Artefacta formed during Fixation of Specimen Thats because MCs lack (desmosomes & Tonofilaments).

DD From Clear spaces of KCs: 1) They show (ex. cell founds Layer of Cyto-plasm peripheral To the Halo.

Special Stains: (خاصة)

(1) Fontan-Masson (MCs لتلوين ميلانين)

(2) DOPA oxidase react

(3) Immunohistochemical (Markers) — S100, Mart-1, HMB 45

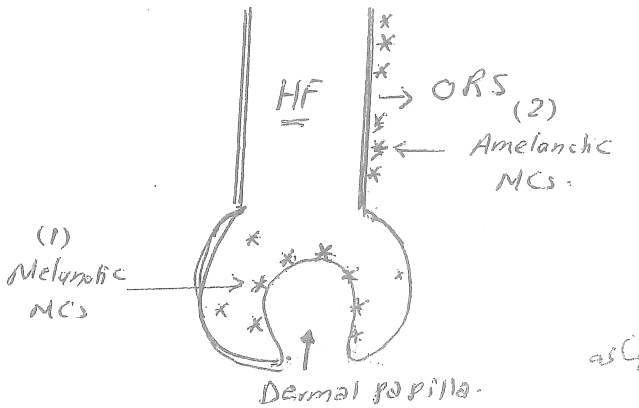
NB DOPA oxidase React: (لتلوين خلايا تكوين الميلانين)

. Most specific Method

. depends on presence of Dopa oxidase (Tyrosinase) enz. inside MCs → so DOPA + Skin Biopsy $\xrightarrow{\text{Tyrosinase}}$ Melanin products (Brown-Black deposits).

(جلد MCs في الجلد) Skin Melanocyte Populations (مجموعات)

- Epidermal MCs
  - ظهارة حرشفية متعددة الطبقات (Basal bet KCs)
- Hair-follicle MCs
  - Melanotic MCs (DOPA +ve)
    - interspersed bet. Matrical cells of HF bulb .. Immediately Capping The dermal Papillae (حليمة الجلد)
    - وظيفتها: اصدار الشعر باللون بتاعه Anagen أثناء
  - Amelanotic MCs (DOPA -ve)
    - Reservior MCs at ORS of HFs.
    - under NL Skin Conditions → inactive
    - under stress (inj. UV, UVL) → Prolif. & migrate to epid. Surface → Perifolli-cular pigmentation (seen on Vitiligo Treated by UVB)



- Q1: what the difference bet. Melanotic & Amelanotic MCs of HFs ??
- Q2 difference bet. epid. MCs & Melanotic MCs of HF → لا تنشط إلا أثناء وقت Anagen.

NB Racial Differences in Skin Color is not caused by differences of MCs Number (both dark & light skinned show KC:MC = 9:1)

But This difference is d/t,

(1). Melanosome difference in { No size, distribution

(2). Type of Melanin { Eumelanin (Brown-black), pheomelanin (Red/white)

In Light Skin

Melanosomes { fewer, smaller, packaged by membrane bound complexes

In dark Skin people

Melanosomes { Much larger, Singly dispersed

Function of Melanocytes

(1) Melanin product { Color of Skin; has Umbrella like act over KCs Nucleus → protect them from UVL & Sc Skin Cancer (So Light skin people اكثر عرضة لسرطانات الجلد); Antioxidant → ↓ UVL effect on Skin.

(2) MCs: Secrete Cytokines & express cell surface Ag ∴ suggest their active role in inflammat?

Disadvantage of Melanin

① يمنع تكوين أشعة الشمس وهذا يسبب نقص في فيتامين د وأيضاً يسبب سرطانات الجلد

② يمنع تكوين VitD ← فيسبب كذا مرض أيضاً في الأطفال أيضاً

•• Melanosomes in Different Colors

Light Skin	Dark Skin
. Stage II Melanosomes	. stage III & IV
. Size < 0.5 µ	. > 0.5 µ
. No/MC < 20	> 20
. distribute: groups	. dispersed (single)
. Degradation: Fast	. Slow

Pathway of epidermal melanin pigmentation

(10 Steps)

1. Migrate of Melanoblasts ⟷ نقص ⟶ . piebaldism . Waardenburg Synd.
2. Differenhate into MCs
3. Mitosis of MCs ⟶ Vitiligo
4. Synthesis of TYR enz. ⟶ Albinism
5, 6, 7. Synthesis of Melanosome ⟶ Chediak Higashi, Ash Leaf of TSC.
8. Melanosomes Melanization ⟶ Albinism, PVC, IGH
9. Melanosome Transfer ⟶ نقص هنا ⟶ . Chediak H. . Nevus depigment. . PVC . Pit. Alba.
10. Melanosome

• Melanin Synthesis

. phenylalanine aa
↓ pha Hydroxylase ⟶ نقص (PKU) (phenyl Ketonuria)
Tryosine
↓
Tyrosinase enz. ⟶ DopA
↓
DopA Quinone
↓
. Pheomelanin — Eumelanin

. Eumelanin	• Pheomelanin
. Ellipsoid melanosomes	. Spherical
. dark (brown-black)	. Contain Cysteine.
	. Light (Yellow or red)

(Basic) للبكتيريا فقط

Types of Skin Color = NL Pigmentation

1. Constitutive : Genetically determined
2. Facultative (Inducible) ← UVR / Hormones

- Caucasoids → white
- Mongoloid → Oriental
- Negroid → Black
- Australoid → Aboriginal

Control & Regulation of Skin Pigmentation

(1) Genetic factors (Constitutive)

(2) UVL : ↑ MCs, ↑ Melanosomes, ↑ Tyr. enz activity

(3) Immediate Pigment darkening (IPD) & delayed Tanning (see Light & Skin).

(4) Endocrinal : α-MSH, ACTH, Estrogen.

(5) Biochemical Factors : IL1 α & β, IL6 & TGFβ

Enzymes & proteins involved in Melanogenesis.

- Tyrosinase enz.
- Tyrosinase Related protein (TRP1 & 2)
- Melanocortin Receptors (MCR1)
- MITF = Microphthalmia associated Transcription Factor
  (if Mutate) → (Waardenburg & Tietz Synd.)

Stages of Melanosomes Development (4)

- Stage I → Spherical No Melanin
- Stage II → Oval, great activity of Tyrosinase.
- Stage III : as stage II + Moderate deposit of Melanin.
- Stage IV : oval, little activity of Tyr., Much Melanin.